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INDEX TO VOLUME 2

Entries in heavy type refer to Special Contributions. The figures after each entry are the serial numbers of individual items; page numbers are not used in the Index

A

- ABRAHAM, E. P. & CHAIN, E.: An enzyme from bacteria able to destroy penicillin, 210
 — Purification and some physical and chemical properties of penicillin, 227
 BAKER, W. & ROBINSON, R.: Penicillamine, characteristic degradation product of penicillin, 230
 — FLETCHER, C. M., FLOREY, H. W., GARDNER, A. D., HEATLEY, N. G. & JENNINGS, M. A.: Further observations on penicillin, 212
 Abscess, cerebral, bacteriology, 604
 Acne bacillus, isolation with penicillin, 208
 Acridines, contra-indications to use on fresh wounds, 344, 342
 — local antiseptic action, 340
 Adrenaline, effect following administration by implantation, 398
 Aerosols: see Air, disinfection
 Africa, nutrition in, 485
 — staple diet, effect on rats, 545
 Agglutination and agglutinins, 420
 Agglutinin, artificial, in blood-group A, 422
 AGNEW, A. P. & KYLES, W. B.: Typhus fever in Gt. Britain, 574
 Agranulocytosis following arsenotherapy, 468
 Air, disinfection, 557, 585, 586, 587, 588
 ALBERT, M. & MITCHELL, W. R. D.: Volkmann's ischaemia of the leg, 417
 ALEXANDER, F.: Study of the distribution of sulphamylamide, 319
 ALLEN, I.: see KING, J. D. et al., 530
 ALLIBONE, E. C. & BAAR, H. S.: Fibrinogen deficiency as a factor in hemorrhagic disease, 475
 ALLOTT, E. N., CRUICKSHANK, R., CYRLAS-WILLIAMS, R., GLASS, V., MEYER, I. H., STRAKER, E. & TEE, G.: Infection of cat-bite and dog-bite wounds with *Pasteurella septica*, 596
 ALMEYDA, J.: see WILLIS, F. E. S. & ALMEYDA, J., 267
 Aluminium, failure to prevent experimental silicosis, 254
 Amblyopia due to vitamin deficiency, 524
 diAminides: see Diaminides; Pentamidine; Phenamidine; Propamidine; Stilbamidine
 Amino-acids, assay, microbiological methods, 486
 — relation to trauma and wound-healing, 486
 — requirements, 486
 — therapeutic effects, 486
 p-Aminobenzoic acid, synergistic effect on penicillin, 221
 Anæmia, 439-461
 — aplastic and hypoplastic, recent work on, 423
 — following arsenotherapy, 468
 — chronic, determination of blood volume in, 479
 — destruction of transfused erythrocytes in, 450
 — erythroblastic, of childhood, 459
 — from nutritional iron deficiency, 439, 440, 441, 442
 — hemolytic, 447, 448, 449
 — acute, with auto-agglutination and auto-hemolysis, 449
 — recent work on, 423
 — hypochromic, recent work on, 423
 — in children, treatment with iron and ascorbic acid, 443
 — in infants and children, blood regeneration rate in, 451, 452
 — in infections, 458
 — macrocytic, treatment with autolysed yeast, 446
 — megaloblastic, in pregnancy and puerperium, 457
 — of pregnancy, hematological study of 48 cases, 456
 — pernicious, recent work on, 423
 — treatment with liver preparation, 444
 — recent work on, 423
 — refractory, 453, 454, 455
 — treatment with erythrocyte transfusions, 460, 461
 Anærobic infections, effect of penicillin on, 215, 216, 217
 Anæsthesia in thoracic surgery, 244
 ANDERSON, D. M.: see TODD, G. S. & ANDERSON, D. M., 262
 ANDERSON, P. H. R., BUCHANAN, J. A. & MACPARTLAND, J. J.: Oiled floors to control respiratory infection: an army experiment, 580
 ANDERSON, T.: Effect of chemotherapy on mortality from pneumonia in Glasgow, 325
 — Some aspects of the chemotherapy of pneumonia, 324
 ANDREWS, C. H.: Virus diseases of man: Review of recent progress, 551
 — & GLOVER, R. E.: Influenza "A" outbreak of October-December, 1943-561
 — HIMMELWEIT, F. & SMITH, W.: Influenza virus as laboratory contaminant, 562
 — KING, H. & VAN DEN ENDE, M.: Chemotherapeutic experiments with viruses of influenza A, lymphogranuloma venereum and vaccinia, 220
 Aneurin, and toxæmia of pregnancy, 354
 — estimation, in National flour and bread, 493
 — methods, 491
 Aneurysm, false, traumatic, treatment of, 393
 — varicose, treatment of, 393
 Anthiomaline in treatment of lymphogranuloma inguinale, 333
 Antibiotics produced by bacteria, 201
 — produced by moulds, 201
 Antibody, incomplete, in anti-Rh sera, 435
 Antigens, bacterial, chemical nature of, 555
 Antimony compounds, in treatment of lymphogranuloma inguinale, 333
 Antiseptic snuffs, 232
 Antiseptics: acridines, local action, 340
 — phenol (phenol), 334
 — proflavine, local action, 340
 Antitoxin in *Cl. welchii* infection, comparison with penicillin, 217

- Apicolysis, extrafascial, and thoracoplasty, 266
 APHORPH, J. O. E.: see FALKNER, N. M. & APHORPH, J. O. E., 357
 ARCHER, G. T. L.: see BAKER, C. G. et al., 568
 Arm, traumatic ischaemia, 416
 ARMSTRONG, T. G.: see JONES, H. E. et al., 533
 Arsenicals, chemical structure in relation to drug resistance of trypanosomes, 303
 — effect of mepacrine treatment on efficacy of, 314
 Arspenamines, agranulocytosis and aplastic anæmia following administration of, 468
 — biological standardization, 295, 332
 Arteries, contusion, treatment of, 393
 — injuries, treatment of, 393
 — peripheral, thrombosis, 413
 — spasm, traumatic, 393, 394, 395
 — types, 394
 Arteriovenous fistula, treatment, 393
 Arteritis, traumatic, 395
 Ascorbic acid: see Vitamin C
 l-Ascorbic acid, 487
 ASLETT, E. A., DAVIES, T. W. & JENKINS, T. I.: Radiological appearances in the development of coal miners' pneumoconiosis, 255
 ATERBIN: see Mepacrine
 Azo colour reaction, for determination of vitamin B₁ in national flour, 494

B

- BAAR, H. S.: Studies in the anæmias of infancy and early childhood. XIII. Experiments on blood regeneration and their significance for the life span of erythrocytes, 452
 — & LLOYD, T. W.: Studies in the anæmias of infancy and early childhood. XII. Regeneration rate of hemoglobin and life span of erythrocytes in normal and pathological conditions, 451
 — see ALLIBONE, E. C. & BAAR, H. S., 475
 Babesiosis, treatment with diamidine, 293
 Bacillus *faecalis*, in sputum, biochemical classification of, 605
 — *pyocyaneus*, as inactivator of penicillin, 225
 — in sputum, biochemical classification of, 605
 Bacteria, antibiotics from, 201
 — antigens of, chemical nature, 555
 — destruction with aerosols: see Air, disinfection
 — enzymes, 592, 593, 594
 — detection in infected tissues, 595
 — Gram-negative, antigens of, 555
 — isolation of specific somatic antigens from, 555
 — Gram-positive, antigens of, 555
 — inhibition of, by penicillin, 200
 — morphological effects of penicillin on, 211
 Bacteriology, development of study of, in Gt. Britain, 550
 — media, selective action of tetrathionate in, 598
 — research and teaching, 550
 Bacteriostasis, slide cell technique for measurement of, 240
 Bacterium *aerogenes*, as inactivator of penicillin, 225
 — *capsulatus*, effect of penicillin on, 237
 — *anaerogenes*, in sputum, biochemical classification of, 605
 — *coli*, as inactivator of penicillin, 225
 — in sputum, biochemical classification, 605
 — *intermedius*, in sputum, biochemical classification of, 605
 — *flexneri*, as inactivator of penicillin, 225
 — *friedländeri aerogenes*, in sputum, biochemical classification of, 605
 — *lactis aerogenes*, effects of resorcinol and m-cresol on growth of, 308
 — growth in presence of sulphonamides, 309
 — morphological and other variations, 307
 — *paratyphum* B, typing with Vi bacteriophage, 552
 — *proteus-morganii*, in sputum, biochemical classification of, 605
 — *typhi-murium*, as inactivator of penicillin, 225
 — *typhosum*, as inactivator of penicillin, 225
 — typing by Vi bacteriophage, 552
 BADCOCK, M.: Speech therapy for certain vocal disorders, 386
 BAKER, A. H. & TWORT, C. C.: Germicidal mists and vapours in air disinfection, 586
 BAKER, C. G., ARCHER, G. T. L. & MITCHELL-HEGGS, G. B.: Enteric typhus fever in Diego Suarez, Madagascar, 568
 BAKER, W.: see ANDERSON, P. H. et al., 230
 BALL, M.: see DREW, W. R. M. et al., 281
 BARANGER, P. & THOMAS, P. E.: Action on avian malaria of the alkaloids of cinchona from the Cameroons and Belgian Congo, 313
 Barbiturates, effects on metabolic processes in central nervous system, 299
 BARCLAY, R. S.: Some observations on eighty consecutive cases of internal pneumonolysis, 263
 BARDHAN, P. N., TYAGI, N. & BOUTROS, K.: Dry blood test for typhus fever: preliminary report, 571
 BARNES, J.: see HAMILTON, W. J. et al., 361
 BARTON-WRIGHT, E. C.: see BOOTH, R. G. & BARTON-WRIGHT, E. C., 495
 — see MACRAE, T. F. et al., 496
 Bayer 7602 (Ac), 317
 BECK, D. J. K.: see RUSSELL, D. S. & BECK, D. J. K., 342
 Beef, nicotinic acid and riboflavin content, 495
 BEGG, A. M., FULTON, F. & VAN DEN ENDE, M.: Inclusion bodies in association with typhus rickettsia, 566
 BELL, G. H. & GUTEMANN, E.: Simple inexpensive photoelectric hemoglobinometer, 470
 Bell, J.: Development of medical studies in Britain: II. The Genetical aspect of disease, 346

- BELT, T. & KING, E. J.: Failure of aluminium to prevent experimental silicosis, 254
 BENJAMIN, B.: see DALEY, W. A. & BENJAMIN, B., 289
 Benzadrine, effect on metabolic processes in central nervous system, 299
 Benzpyrene, carcinogenic action, 306
 Benzyl benzoate, sarcopitolic efficiency, 335
 BIGELOW, W. G. & LANTON, E. C. G.: Some uses for dry cold therapy, and a proposed cooling cabinet, 407
 BIGGER, J. W.: Bacteriological investigations in a mass chest survey, 257
 BINGHAM, K.: see MACKAY, H. M. M. et al., 442
 — see WILLS, L. et al., 441
 BISHOP, P. M. F.: Endocrine therapy in gynaecology and obstetrics, 368
 BLACK, D. A. K., MCCANCE, R. A. & YOUNG, W. F.: Study of dehydration by means of balance experiments, 507
 Blackwood, W.: Injury from exposure to low temperature: pathology, 390
 — A pathologist looks at ischaemia, 414
 — Studies in the pathology of human 'immersion foot', 401
 — & RUSSELL, H.: Experiments in the study of immersion foot, 398
 — see LEARMONTH, J. R. et al., 395, 413
 — see UNGLEY, C. C. & BLACKWOOD, W., 397
 BLAILEY, J. B.: see KNOTT, F. A. & BLAILEY, J. B., 584
 Blast injuries, pathology, 274
 Blood, bacteriostatic power, measurement of, 240
 — concentration of sulphonamides in, 294
 — donors, syncope in, 476, 478
 — effect of penicillin on, 202, 212, 213
 — estimation of vitamin C in, 500
 — group substances, human, nature, 422
 — occurrence in tissues and body fluids, 422, 438
 — groups, 420, 421, 422, 426, 427, 428, 429, 430, 431, 432, 433, 434, 435, 436, 437, 438
 — genetic and forensic implications, 420
 — inheritance, recent observations on, 421
 — plasma, action of coagulase on, 602
 — ascorbic acid level, 487
 — in hospital residents, 503, 504
 — changes during storage, 473
 — clot occlusion of bronchi in treatment of chronic tuberculous cavitation, 270
 — proteins, and hemoglobin production, 486
 — effect on blood sedimentation rate, 472
 — in infants, 471
 — volume, determination by Evans-blue method, 480, 481
 — platelets in experimental thrombocytosis, 462
 — pressure, venous, during venesection and blood transfusion, 477
 — sedimentation rate, effect of plasma proteins on, 472
 — serum, changes during storage, 473
 — proteins, estimation of, 474
 — variations in level of, 474
 — sugar, effect of diamidines on, 316
 — transfusion, history of, 389
 — in anæmia, erythrocyte destruction in, 450
 — in erythroblastosis foetalis, 429
 — incompatible, symptomless, 436
 — venous pressure during, 477
 — vessels, effect of frostbite on, 402
 — peripheral, circulation of, nervous control, 408, 409, 410, 411, 412
 — disorders of, 389
 — injuries to, due to cold, 395, 396, 397, 398, 399, 400, 401, 402, 403, 404
 — reflex vasodilatation in surgery, 411
 — volume, determination after blood loss, 425
 — by Evans-blue method, 480, 481
 — in chronic anæmia, 479
 — restoration after injury, 389
 Blood-brain barrier, relation to efficacy of trypanocides, 298
 BODENHAM, D. C.: Infected burns and surface wounds: value of penicillin, 238
 Bone, infected, radiological picture following penicillin therapy, 202
 — growth, effect of vitamins on, 520, 521
 — marrow, biopsies, in refractory anæmias, 453, 454, 455
 BONEY, V. & MCINDOE, A. H.: Unique constructive operation, 367
 Books, Memoranda, Reports, 290, 344, 370, 387, 418, 482, 548, 606 [An alphabetical list of the books, memoranda and reports reviewed in this volume is given at the end of the Index.]
 Boome, E. J.: The scope of speech therapy, 374
 BOORMAN, K. E. & DODD, B. E.: The group-specific substances A, B, M, N and Rh: their occurrence in tissues and body fluids, 438
 — & MORRISON, P. L.: The incidence of hemolytic disease of the foetus ('erythroblastosis foetalis') in different families: the value of serological tests in diagnosis and prognosis, 432
 BOOTH, R. G. & BARTON-WRIGHT, E. C.: Nicotinic acid and riboflavin in beef extracts and corned beef, 495
 BOURNE, G.: Some experiments on the possible relationship between vitamin C and calcification, 521
 BOUTROS, K.: see BARDHAN, P. N. et al., 571
 BOYCOTT, M.: see POLES, F. C. & BOYCOTT, M., 476
 Brain, abscess, bacteriology, 604
 — lesions, effect on verubaral responses, 381
 — respiration, effect of narcotics on, 299
 BRANSTY, E. R., HUNTER, J. W., MAGEE, H. E., MILLIGAN, E. H. M. & LANTON, E. C. G.: Influence of supplements of vitamins A, B₁, B₂, C and D on growth, health, and physical fitness, 537

Bread, composition, 484
 — vitamin B, content, 493, 494
 — war-time supply in Britain, 492
 Breast: see Lactation
 BRIDGES, R. F.: Note on preparation of suspensions for the Weil-Felix test, 573
 Bright's disease, plasma amino-acid level in, 486
 Britton, C. J. C.: Recent work on anaemias, 423
 Brock, R. C.: The present position of thoracic surgery, 244
 — Bronchial anatomy and the surgery of lung abscess, 247, 248
 — Interlobar fissures of the lungs, 250
 — Surgical treatment of bronchial carcinoma, 259
 — HODGKISS, F. & JONES, H. O.: Bronchial embolism and posture in relation to lung abscess, 249
 BROCKBANK, W. & WHITTAKER, S. R. F.: Notes on typhus fever in the Middle East, 570
 Bronchiectasis, lobectomy and pneumonectomy in, 244
 Broncho-alveolar cysts, 261
 Bronchus, anatomy, diagrammatic summary of, 246
 — recent work on, 245
 — and surgery of lung abscess, 247, 248
 — artificial occlusion, in treatment of chronic tuberculous cavitation, 270
 — carcinoma, pneumonectomy in, 244
 — surgical treatment, 259
 — posture in relation to embolism and lung abscess, 249
 BROOKS, W. D. W.: Early diagnosis of new growths of the lung, 260
 BROWN, G. M., HAYWARD, O. C., POWELL, E. O. & WITTS, L. J.: Destruction of transfused erythrocytes in anaemia, 450
 BROWNE, F. J.: Reactions to pressor substances in normal and toxæmic women, 355
 BUCHANAN, J. A.: see ANDERSON, P. H. R. *et al.*, 580
 BURN, J. H. & WITHELL, E. R.: A principle in raspberry leaves which relaxes uterine muscle, 353
 BURNETT, C. W. F.: see HARTLEY, J. B. & BURNETT, C. W. F., 362, 363
 Burns, effect of penicillin and propamidine on, 234
 — infected, effect of penicillin on, 238
 — protein loss in, 486
 BURROWS, H.: Nomenclature of hormone-producing tumours of the ovary, 369

C

Calcium absorption, effect of National Wheatmeal on, 512
 — effect of protein derivatives on, 514
 — carbonate, antirachitogenic power in rats, 513
 — metabolism, seasonal and annual changes, 511
 — phosphate, antirachitogenic power in rats, 513
 — role in nutrition, 489
 — war-time supply in Britain, 492
 Calorie requirements, 486
 Calories, war-time supply in Britain, 492
 CAMPBELL, J. A.: Lung tumours in mice and man, 253
 Cancer, pulmonary, in mice and man, 253
 CAPPELL, D. F.: see RACE, R. R. *et al.*, 426
 Carboxyhaemoglobin, determination of, 424
 Carcinogenic action of benzpyrene, 306
 Caries, dental, effect of fluorine on, 525, 526, 527, 528
 — nutritional factors, 490
 CARTWRIGHT, J. A.: see KAPFELER-ADLER, R. & CARTWRIGHT, J. A., 354
 CATCH, J. R., COOK, A. H. & HEILBRON, I. M.: Purification and chemistry of penicillin, 229
 Catechol, as air disinfectant, 585
 CAWTHORNE, T. E.: Treatment of Ménière's disease, 383
 — FITZGERALD, G. & HALLPIKE, C. S.: Studies in human vestibular function. II. Observations on the directional preponderance of caloric nystagmus ("Nystagi usbereitschaft") resulting from unilateral labyrinthectomy. III. Observations on the clinical features of Ménière's disease: with special reference to the results of caloric tests, 381
 Cerebrospinal fever: see Meningitis
 — fluid, relation to efficacy of trypanocides, 298
 — fluid, trypanocidal power, 298
 CHADWICK, V.: see JONES, H. E. *et al.*, 533
 Chain, E.: Antibacterial substances [other than penicillin] from bacteria and moulds, 201
 — & FLOREY, H. W.: Discovery of the chemotherapeutic properties of penicillin, 199
 — GARDNER, A. D., HEATLEY, N. G., JENNINGS, M. A., ORR-EWING, J. & SANDERS, A. G.: Penicillin as a chemotherapeutic agent, 209
 — see ABRAHAM, E. P. & CHAIN, E., 210, 227
 — see ABRAHAM, E. P. *et al.*, 212, 230
 CHALLINOR, S. W. & DUGUID, J. P.: Propylene glycol vapour as an air disinfectant: I, 587
 — & MACNAUGHTAN, J.: The production of penicillin, 223
 — see DUGUID, J. P. & CHALLINOR, S. W., 588
 Chemotherapy, relations between *in vivo* and *in vitro* actions of drugs, 300
 Chest diseases, rehabilitation in, 276
 — injuries, closed, pathology of, 273
 — surgery, 273, 274
 — scope of, 275
 — war wounds and injuries, 271, 272
 CHICK, H. & CUTTING, M. E. M.: Nutritive value of the nitrogenous substances in the potato as measured by their capacity to support growth in young rats, 518
 CHICK, H.: see PETERS, R. A. *et al.*, 493
 Childhood infection, relation to adolescent and adult pulmonary tuberculosis, 282
 Children, anaemia in, blood regeneration rate in, 451, 452
 — due to war-time diet, 441, 442
 — erythroblastic, 459
 — treatment with iron and ascorbic acid, 443
 — deaf and dumb, education of, 378, 379
 — dentition, improvement since 1929...526
 — Gibraltor, gingival disease in, 530
 — nutritional state, 539, 540
 — pulmonary tuberculosis in, 282, 283, 284
 — vitamin A and C levels in, 535
 Choline, lipotropic action, 486
 CHRISTOPHERS, S. R.: Cell metabolism of the malaria parasite in relation to the mode of action of antimalarial drugs, 297

Cinchona alkaloids, value in avian malaria, 313
 Circulation, dynamics of, 425, 476, 477, 478, 479, 480, 481
 CLARK, A. M., COLEBROOK, L., GIBSON, T., THOMSON, M. L. & FOSTER, A.: Penicillin and propamidine in burns: elimination of haemolytic streptococci and staphylococci, 234
 CLARKE, A. G. & PRESCOTT, F.: Studies in vitamin B deficiency with special reference to mental and oral manifestations, 516
 CLEGG, J. W. & KING, E. J.: Estimation of haemoglobin by the alkaline haematin method, 469
 CLELAND, W. P. & RACKOW, A. M.: Radiology in post-operative chest surgery, 278
 — see THOMAS, C. P. & CLELAND, W. P., 266, 267
 CLIFFORD-JONES, E. & MACDONALD, N.: Pneumoperitoneum in collapse therapy of pulmonary tuberculosis, 264
 CLIVE, F. T.: Mass radiography in women: review of 30,000 examinations, 279
Clostridium welchii, effect of penicillin on, 215, 216, 217, 237
 CLUTTERBUCK, P. W., LOVELL, R. & RAISTRICK, H.: Formation from glucose by members of the *Penicillium chrysogenum* series of a pigment, an alkali-soluble protein and penicillin—the antibacterial substance of Fleming, 206
 Coagulase, nature and mode of action, 602
 COHEN, S. M.: Traumatic arterial spasm, 394
 Cold, common, pulmonary complications, 277
 — in treatment of damage due to cold, 405, 406, 407
 — injury from exposure to (pathology, clinical features, prevention, treatment), 390, 391, 392
 — vasomotor disorders of limbs from, 395, 396, 397
 COLEBROOK, L.: see CLARK, A. M. *et al.*, 234
 COLLIER, H. O. J.: see LOURIE, E. M. & COLLIER, H. O. J., 314
 Complement activity, and vitamin C intake, 501
 Conception, season of, relation to intelligence, 360
 Concussion deafness, 380
 COOK, A. H.: see CATCH, J. R. *et al.*, 229
 COOK, R. P., DAVIDSON, W. A., KEAY, D. M. & MCINTOSH, D. G.: Midday school meal: study of its relation to total weekly dietary of a group of schoolboys, 547
 Cooley's anaemia in Cyprus, 459
 Cooling cabinet, for dry cold therapy, 405, 406, 407
 COPPING, A. M.: see MACRAE, T. F. *et al.*, 496
 CORBETT, H. V.: see GOLDSTONE, B. W. & CORBETT, H. V., 400
 Cornea, effect of nutritional deficiency on, 522, 523
 Corpuscle-haemoglobin method for blood volume determination in chronic anaemia, 479
Corynebacterium acnes, isolation with penicillin, 208
 COUMOULOS, H.: see MELLANBY, M. & COUMOULOS, H., 526
 COWARD, K. H.: see PETERS, R. A. *et al.*, 493
 CRADDOCK, S.: Use of penicillin in cultivation of *acne bacillus*, 208
 CRAIG, A. A., LEWIS, F. J. W. & WOODMAN, D.: Survey of vitamin-C level in wartime in-pregnant women, 502
 Craniolacunia, 362, 363
 m-Cresol, effect on growth of *Bact. lactis aerogenes*, 308
 CROFT, P. G.: see RICHTER, D. & CROFT, P. G., 499, 500
 Cross-infection in hospitals, 553, 554, 575, 576, 577, 578, 579, 582, 584
 CROWLEY, N.: Hyaluronidase production by haemolytic streptococci of human origin, 593
 Cruickshank, R.: Hospital infection: historical review, 553
 — see ALLOTT, E. N. *et al.*, 596
 — see WRIGHT, J., *et al.*, 578
 Cultures, National Collection of, 556
 CURD, F. H. S.: Activity of drugs in malaria of man, monkeys and birds, 312
 CURRIE, J. P.: Acute haemolytic anaemia: case presenting hitherto unreported features, 449
 Cuthbertson, D. P.: Protein metabolism, 486
 CUTTING, M. E. M.: see CHICK, H. & CUTTING, M. E. M., 518
 Cyanmethaemoglobin, determination of, 424
 Cyprus, erythroblastic anaemia among children in, 459
 CYRLAS-WILLIAMS, R.: see ALLOTT, E. N. *et al.*, 596

D

DALEY, W. A. & BENJAMIN, B.: Tuberculosis in London, 289
 DAVIDSON, L. S. P., DAVIS, L. J. & INNES, J.: Megaloblastic anaemia of pregnancy and puerperium, 457
 — Studies in refractory anaemia. I. Technique and interpretation of sternal puncture biopsies. Classification, 453; II. Anaemias with hypocellular, normoblastic marrows, 454; III. Refractory anaemias with cellular marrow, 455
 — & DONALDSON, G. M. M.: Treatment of anaemia in school-children with iron and ascorbic acid, 443
 — DYAR, M. J., LINDSAY, S. T. & MCSORLEY, J. G.: Nutritional iron deficiency anaemia in war-time. I. The haemoglobin levels of 831 infants and children, 439
 — LINDSAY, S. T. & MCSORLEY, J. G.: Nutritional iron deficiency anaemia in war-time. II. The haemoglobin levels of 3,338 persons from birth to 55 years of age, 440
 — see DAVIS, L. J. *et al.*, 444
 — see MACRAE, H. M. M. *et al.*, 442
 — see MCSORLEY, J. G. & DAVIDSON, L. S. P., 445
 DAVIDSON, W. A.: see COOK, R. P. *et al.*, 547
 DAVIES, D. S. & HINSHELWOOD, C. N.: Adaptation of *Bact. lactis aerogenes* to growth in presence of sulphonamides, 309
 DAVIES, T. J.: see ASLETT, E. A. *et al.*, 255
 DAVIS, L. J.: Determination of blood volume in man with Evans-blue ("T-1824"), 480
 — Haemolytic anaemias, 447
 — Symptomatic haemolytic anaemia: report of 4 cases, 448
 — DAVIDSON, L. S. P., RIDING, D. & SHAW, G. E.: Treatment of pernicious anaemia with an experimental proteolysed liver preparation: preliminary observations, 444
 — see DAVIDSON, L. S. P. *et al.*, 453, 454, 455, 457
 Deaf, pioneer teachers of, 375
 Deaf-mutism, 375, 377, 378, 379
 Deafness from concussion, 380
 — in infancy and childhood, 377, 378, 379

DEANESLY, R. & PARKES, A. S.: Deposition of protein material in implanted pellets of steroid hormones, 339
 Dehydration, balance experiments, 507, 508
 — in infants, 509
 DELAFIELD, M. E., STRAKER, E. & TOPLEY, W. W. C.: Antiseptic snuffs, 232
 Dental caries, effect of fluorine in, 525, 526, 527, 528
 — nutritional factors, 490
 Dermatitis, following local application of sulphonamides, 322
 Detergents: phemeride (phemerol), 534
 DE WAAL, H. L.: Wound infection: preliminary note on combined clinical and bacteriological investigation of 708 wounds, 591
 Diamidines, in treatment of protozoal infections, 293
 — in treatment of babesiasis, 293
 — metabolic effects, 316
 — toxicity, 293
 — trypanocidal, pharmacological action of, 315
 — see also Pentamidine; Propamidine; Stilbamidine
 DICKSON, E. D. D.: see JOHNSON, T. B. *et al.*, 384
 Diet, effect on reproduction and lactation, 364
 — in war-time, relation to anaemia, 439, 440, 441, 442
 Dimethylthianthrene, sarcotocidal efficiency, 335
 Diphtheria, laboratory diagnosis, 599
 Disinfection, aerial: see Air, disinfection
 DOBBS, R. H.: see MACRAE, H. M. M. *et al.*, 442
 — see WILLS, L. *et al.*, 441
 — see YOUNG, W. F. *et al.*, 509
 DODD, B. E.: see BOORMAN, K. E. & DODD, B. E., 438
 — see BOORMAN, K. E. *et al.*, 432
 DODDS, G.: see HAMILTON, W. J. *et al.*, 361
 DONALDSON, G. M. M.: see DAVIDSON, L. S. P. & DONALDSON, G. M. M., 443
 — see DAVIDSON, L. S. P. *et al.*, 439, 440
 DONNELLY, T. H., HUGHES, H. P., ROBERTSON, D. & PHILLIPS, E.: Influenza "A": account of a minor epidemic, 560
 DREW, W. R. M., SAMUEL, E. & BALL, M.: Primary atypical pneumonia, 281
 Droplet infection, 553
 Drug action, and chemical constitution, 302
 — insecticidal, 304
 — physico-chemical aspects, 301
 Drugs, antagonism by neutralisation and competition, 296
 — antimalarial, tests for efficacy of, 312
 — modes of action, 296, 297, 298, 299, 300, 301, 302, 303, 304, 305, 306, 307, 308, 309
 — new, evaluation of, in Britain, 292
 — relations between *in vivo* and *in vitro* actions, 300
 DRUMMOND, R.: Symptomless incompatible transfusion and resultant changes in iso-agglutinin titre, 436
 DUFFIN, W. M. & SMITH, S.: Penillic acid, an optically active acid from penicillin, 231
 DUGUID, J. P. & CHALLINOR, S. W.: Propylene glycol vapour as air disinfectant. II, 588
 — see CHALLINOR, S. W. & DUGUID, J. P., 587
 DUNCAN, J.: see WOKES, F. *et al.*, 498
 Dust, as vehicle of infection in hospital wards, 575, 576, 577, 578, 579
 — transmission of infection by, prevention of, 553
 "Dust-reticulation" disease of lungs, 243
 Dusts causing lung diseases, 243, 253, 254, 255
 DYAR, M. J.: see DAVIDSON, L. S. P. *et al.*, 439
 Dysentery, bacillary, treatment with sulphaguandine, 328
 DYSON, M. & PLAUT, G.: Study of the accuracy of serum protein estimations and of diurnal variations in their level, 474

E

Ear, influence of vitamins on, 376
 — internal, 381, 382, 383
 Eclampsia, placenta in, 357
 EDGEcombe, C. N.: see MCCANCE, R. A. *et al.*, 515
 EDWARD, D. G. ff.: Haemolytic streptococci in the dust of hospital wards, and their relationship to infection, 576
 — & LIDWELL, O. M.: Studies on air-borne virus infections. III. The killing of aerial suspensions of influenza virus by hypochlorous acid, 557
 EDWARDS, A. T.: War wounds and injuries of the chest, 271
 EDWARDS, C. W.: see HARWOOD, F. G. *et al.*, 579
 EDWARDS, F. R.: Rehabilitation of the chest case, 276
 EISEN, A.: see HEAF, F. R. G. *et al.*, 336
 Electrocardiogram, effect of administration of antimalarials on, 311
 ELLIOTT, G. A.: Anaemias of pregnancy: report on haematological study of 48 cases of pregnancy with a review of the literature, 456
 Elliprocystosis and hereditary haemorrhagic telangiectasia, 465
 Embolism, pulmonary, relation to posture, 249
 Embryo, human, early development, 361
 Empyema, after-treatment, 244
 Encephalitis virus, transmission, 551
 Endocrine therapy in gynaecology and obstetrics, 368
 Endometrium, tuberculosis, 359
 Energy expenditure and protein intake, 486
 Enteric fever: see Typhoid
 Enteritis, epidemic, neonatal, treatment with sulphaguandine, 327
 Enzymes, bacterial, 592, 593, 594
 — detection in infected tissues, 595
 — of, 467
 — promoting involution of postpartum uterus, 350
 Erythroblastosis foetalis, and the Rh factor, 426, 427, 428, 429, 430, 431, 432, 433
 — incidence, 432, 433
 — macroscopic and microscopic findings in, 434
 — survival of transfused erythrocytes in, 429
 — treatment with Rh-negative blood, 427
 Erythrocytes, agglutination by viruses, 551
 — elliptical, in hereditary haemorrhagic telangiectasia, 465
 — life span, in anaemias of infants and children, 451, 452
 — transfused, destruction in anaemia, 450
 — in treatment of anaemia, 460, 461
 — survival in haemolytic disease of the newborn, 429

tetra-ethylthiuram monosulphide; sarcopticidal efficiency, 335
Eugenol carbonyl, as air disinfectant, 585
EVANS, H. & PERRY, K. M. A.: Thrombocytopenic purpura, 462
Evans-blue method of blood volume determination, 480, 481
EWING, A. W. G.: Nature of deaf-mutism—childhood and adolescence, 378
— see FRANKLIN, P. *et al.*, 379
EWING, I. R.: Deafness in infancy and early childhood, 377
— see FRANKLIN, P. *et al.*, 379
Eye, and nutritional deficiency, 522, 523, 524
— experimental lesions, effect of penicillin on, 218, 219
— infections, effect of penicillin on, 233

F

Fainting in blood donors, 476, 478
FALCONER, M. A.: see RUSSELL, D. S. & FALCONER, M. A., 340
FALKNER, N. M. & ARTHUR, J. O. E.: The placenta in eclampsia and nephritic toxæmia, 357
Fallopian tubes, estimation of patency, 359
Family, size, and nutritional state, 542
Fat, war-time supply in Britain, 492
Fatigability and protein intake, 486
FAWDRY, A. L.: Erythroblastic anaemia of childhood (Cooley's anaemia) in Cyprus, 459
Feeding, communal, 546, 547
— in war-time Britain, 492
Felix, A.: Modern laboratory methods in the control of typhoid and paratyphoid-B fever, 552
— Technique and interpretation of Weil-Felix test in typhus fever, 572
FERGUSON, J. W.: Agranulocytosis and aplastic anaemia after arsenamines, 468
FERGUSON, W. J. W.: Ocular signs of riboflavin deficiency, 522
Fibrinogen deficiency, as factor in hæmorrhagic disease, 475
FINCH, E.: see HICKMANS, E. M., FINCH, E. & TONKS, E., 471
FINDLAY, L.: see MACKAY, H. M. *et al.*, 442
FITZGERALD, G. & HALLPIKE, C. S.: Studies in human vestibular function. I. Observations on the directional preponderance ("Nystagmus-berücksichtigung") of caloric nystagmus resulting from cerebral lesions, 381
— see CAWTHORNE, T. E. *et al.*, 381
Fleming, A.: Discovery of penicillin, 198
— Penicillin for selective culture and for demonstrating bacterial inhibitions, 200
— Antibacterial action of cultures of a penicillium with special reference to their use in the isolation of *B. influenzae*, 203
— *In vitro* tests of penicillin potency, 214
— Specific antibacterial properties of penicillin and potassium tellurite, 205
— Streptococcal meningitis treated with penicillin: measurement of bacteriostatic power of blood and cerebrospinal fluid, 236
— & MACLEAN, I. H.: Occurrence of influenza bacilli in the mouths of normal people, 204
FLEMING, G. B.: Incidence and treatment of tuberculosis in children, 284
FLETCHER, C. M.: see ABRAHAM, E. P. *et al.*, 212
Flexner dysentery, treatment with sulphaguanidine, 328
Flies, as vectors of *Strept. haemolyticus*, 581
FLOREY, H. W. & JENNINGS, M. A.: Some biological properties of highly purified penicillin, 213
— see ABRAHAM, E. P. *et al.*, 212
— see CHAIN, E. & FLOREY, H. W., 199
— see CHAIN, E. *et al.*, 209
— see FLOREY, M. E. & FLOREY, H. W., 233
FLOREY, M. E.: Clinical uses of penicillin, 202
— & FLOREY, H. W.: General and local administration of penicillin, 233
Flour unit of penicillin potency, 239
Flour, national, effect on calcium absorption, 512
— vitamin B, content, 493, 494
Fluids, effects of reduced intake, 507, 508
Fluorine and dental caries, 490, 527, 528
— effect on incidence of mottled enamel, M-hypoplasia and dental caries, 525, 526, 527, 528
Fetus, effects of sulphonamides on, 294
Food policy in war-time, 484, 492
— preparation, methods, effects on nutritional state, 485
Foot, effect of cold on: see Frostbite; Immersion foot
FOSTER, A.: see CLARK, A. M. *et al.*, 234
Foster-Carter, A. F.: Recent work on the anatomy of the bronchi, 245
— Summary in diagram of the anatomy of the bronchi and broncho-pulmonary segments, 246
FOWKE, H.: The effect of supplements of vitamins and minerals on the health of girls, 536
FOWLER, E. P.: see JOHNSON, T. B. *et al.*, 384
Fractures, compound, treatment with penicillin, 237
FRANCKLYN, A. B.: see KING, J. D. *et al.*, 530
FRANKAU, I. M.: Acceleration of co-ordinated muscular effort by nicotinamide: preliminary report to Medical Research Council, 543
FRANKLIN, L. M.: see HEAF, F. R. G. *et al.*, 336
FRANKLIN, P., GUTHRIE, D., EWING, I. R. & EWING, A. W. G.: Discussion on deaf-mutism, 379
FREEMAN, W.: see WIEN, R. *et al.*, 316
Freezing, effect on limbs, 390, 391, 392
Frostbite, clinical features, prevention, treatment, 392
— pathology of, 390
— prevention, 403, 404
— treatment, 403, 404
— by low temperature, 405, 406, 407
— by sympathectomy, 412
— vascular changes in, 402
FULTON, F.: see BEGG, A. M. *et al.*, 566
FULTON, J. D.: Comparison of the biological action of Bayer 7602 (Ac) and the corresponding I.C.I. synthetic product, 317
— & YORKE, W.: Studies in chemotherapy. XXXIV. Comparison of the results obtained by different methods of administration of drugs in trypanosomal infections in mice, 337

G

GADDUM, J. H.: Biological aspects [of drug action]: the antagonism of drugs, 296
GARDINER, P. A.: see LYLE, T. K. *et al.*, 523

GARDNER, A. D.: Morphological effects of penicillin on bacteria, 211
— see ABRAHAM, E. P. *et al.*, 212
— see CHAIN, E. *et al.*, 209
Garrod, L. P.: Penicillin: Its properties and powers as a therapeutic agent, 197
— Some observations on hospital dust with special reference to light as a hygienic safeguard, 577
— Treatment of war wounds with penicillin, 237
Gas gangrene, treatment with penicillin, 215, 216, 217, 237
Gastric juice, blood-group substances from, 422
— examination, value in diagnosis of pulmonary tuberculosis, 257, 258
Gastro-enteritis, epidemic, neonatal, treatment with sulphaguanidine, 327
GAYLOR, J. B.: see LEARMONTH, J. R. *et al.*, 395
GELL, P. G. H.: see KNOX, R. *et al.*, 598
Genetics in disease, development of study in Britain, 346
GIBSON, T. P.: see CLARK, A. M. *et al.*, 234
GILDING, H. & NUTT, M. E.: Changes occurring in plasma and serum on storage and their physiological effects, 473
GILMAN, J.: Effects on rats of prolonged feeding with the staple African diet, 545
GILMOUR, J. R.: Erythroblastosis foetalis, 434
GIMSON, J. D.: Hemolytic disease of the newborn (erythroblastosis foetalis): treatment with Rhesus-negative blood, 427
Gingivitis in Gibraltar evacuee children, 530
— in naval ratings, 529
— in Royal Air Force, 531
— nutritional factors, 490
GISSANE, W., MILES, A. A. & WILLIAMS, R. E. O.: Design of dressing stations and control of wound infection, 583
GLASS, V.: see ALLOTT, E. N. *et al.*, 596
GLOCK, G. E.: see PLATT, B. S. & GLOCK, G. E., 494
GLOVER, R. E.: see ANDREWES, C. H. & GLOVER, R. E., 561
— see ANDREWES, C. H. *et al.*, 562
— see STUART-HARRIS, C. H. *et al.*, 559
GOLDSTONE, B. W. & CORBETT, H. V.: Aetiology of "immersion foot", 400
Gonadotrophin, chorionic, effect following administration by implantation, 338
GOODALL, A. L.: Transfusion of cell concentrates, 461
GORDON, C. M. & WARDLEY, J. R.: Effect of plasma proteins upon sedimentation rate of human blood, 472
GORDON, G.: Mechanism of the vasomotor reflexes produced by stimulating mammalian sensory nerves, 408
GORDON, R. M. & UNSWORTH, K.: Lethal action of benzyl benzoate, dimethylthianthrene ("Mitigal") and tetra-ethylthiuram monosulphide ("Tetmos") on the scabies-producing mites, *Notodres* sp. and *Sarcoptes scabiei* var. *hominis*, when tested *in vitro*, 335
Gorse extracts, effect on uterus, 352
GOUGH, J.: see THOMAS, D. *et al.*, 270
GOWAR, F. J. S.: Carcinoma of lung: Value of sputum examination in diagnosis, 256
Gramicidin, 201
Great Britain, war-time food policy, 492
Green, F. H. K.: Clinical evaluation of new remedies in Britain, 292
GREEN, H. F.: see JONES, H. E. *et al.*, 533
GREEN-ARMYTHA, V. B., WALKER, K. & WITTKOWER, E. W.: Discussion on new developments in the investigation and treatment of sterility, 358
GREENE, R.: Cold in the treatment of damage due to cold, 405
— Immediate vascular changes in true frostbite, 402
— see LEARMONTH, J. R. *et al.*, 395
— see MELLANBY, E. *et al.*, 376
GRIFFITHS, D. L.: Volkmann's ischaemic contracture, 415
Growth, at home and at school, 538
— effect of vitamin supplements on, 537
GUIDE TO THE JOURNALS, 291, 345, 371, 388, 419, 483, 549, 607
Gums, bleeding, in naval personnel, 529
— incidence in R.A.F., 532
GUNN, W.: see WRIGHT, J. *et al.*, 578
GUTHMANN, E.: see BELL, G. H. & GUTHMANN, E., 470
Guthrie, D.: Development of medical studies in Britain: IV. Oto-laryngology, 372
— Pioneers in the teaching of the deaf, 375
— see FRANKLIN, P. *et al.*, 379
— see JOHNSON, T. B. *et al.*, 384
Gynaecology, development in Britain, 347

H

Hæmatin, alkaline, in blood, determination of, 424
Hæmoglobin and plasma proteins, 486
— determination, photoelectric methods, 424
— estimation by alkaline hæmatin method, 469
— levels of infants, children and adults, 439, 440
— regeneration rate in anæmias of infants and children, 451, 452
Hæmoglobinometry, photoelectric, 470
Hæmoglobinopathy, clinical, 424, 469, 470
Hæmolytic disease of newborn: see Erythroblastosis foetalis
Hamophilus influenzae, incidence in mouths of normal people, 204
— effect of ————
— isolation
— pertussis, inhibit
— isolation
Hæmorrhage, circulatory dynamics of, 425
— concealed accidental, renal complications, 356
— control of, history of, 389
— immediate effects, 425
— late effects, 425
— spontaneous suppression in traumatic arterial spasm, 394
Hæmorrhagic disease of newborn, 464
— fibrinogen deficiency in, 475
HALE, J. H.: see SMITH, W. & HALE, J. H., 602
HALL, T. C. & LEHMANN, H.: Experiments on the practicability of increasing calcium absorption with protein derivatives, 514
Hallpike, C. S.: Notes on the progress and future role of research in otology, 373
— Investigation of Ménière's disease, 382
— see CAWTHORNE, T. E. *et al.*, 381
— see FITZGERALD, G. & HALLPIKE, C. S., 381

HAMILTON, W. J., BARNES, J. & DODDS, G.: Phases of maturation, fertilization and early development in man, 361
Hand infections, treatment with penicillin, 202
Hands, sterility, relative, among metal workers, 603
HARPER, G. J.: Inhibition of penicillin in routine culture media, 225
HARRIS, L. J.: see PETERS, R. A. *et al.*, 493
Hart, P. M. D'A.: Medical and social aspects of pulmonary disease, 243
HARTLEY, J. B. & BURNETT, C. W. F.: A study of craniofacial, 362
— New light on the origin of craniofacial, 363
HARWOOD, F. G., POWNEY, J. & EDWARDS, C. W.: New technique for application of dust-laying oils to hospital bed-clothes, 579
HAVENS, W. P.: see PAUL, J. R. *et al.*, 564
Hawking, F.: Note on the biological standardisation of neoparsphenamine, 295
— Recent work on the pharmacology of sulphonamides, 299
— Histological effect of proflavine powder on fresh wounds, 34
— Intramuscular injection of mepacrine (atebrin); histological effect, 343
— Local action of sulphonamides, 318
— Standardisation of the therapeutic potency of neoparsphenamine and sulpharsphenamine, 332
HAYWARD, O. C.: see BROWN, G. M. *et al.*, 450
Head, wounds, treatment with penicillin, 237
HEAF, F. R. G., HURFORD, J. V., EISER, A. & FRANKLIN, L. M.: Tuberculosis treated with promin, 336
— see SNELL, W. E. *et al.*, 280
Hearing: see Deaf; Ear
Heart, output, effect of various factors on, 425
HEATH, F. K.: see TURNER, J. C. *et al.*, 222
HEATLEY, N. G.: see ABRAHAM, E. P. *et al.*, 212
— see CHAIN, E. *et al.*, 209
HEILBRON, I. M.: see CATCH, J. R. *et al.*, 229
HEIMANN, H. L. & SHAPIRO, B. G.: Effects of plasmaquin, atebirin, and quinacine on the electrocardiogram, 311
HELLER, H.: Renal function of newborn infants, 510
Helvolic acid, 201
HENDERSON, J. L.: Sulphaguanidine in neonatal epidemic gastro-enteritis, 327
HENDERSON, P.: Speech defects, 385
HENRY, K. M.: see MACRAE, T. F. *et al.*, 519
Hepatitis, infective, role of proteins in treatment of, 486
Heredity in disease, development of study in Britain, 346
Hexyl resorcinol, as air disinfectant, 585, 586
HICKMANS, E. M., FINCH, E. & TONKS, E.: Plasma protein values in infants, 471
HIMMELWEIT, F.: see ANDREWES, C. H. *et al.*, 562
HINSHELWOOD, C. N.: see DAVIES, D. S. & HINSHELWOOD, C. N., 309
— see LODGE, R. M. & HINSHELWOOD, C. N., 307
HOARE, E. D.: Occurrence of Rh antigen in the population: notes on 5 cases of erythroblastosis foetalis, 428
O'BRIEN, J. R. & WATKINS, A. G.: Dust as vehicle of infection in children's wards, 575
HOBBS, B. C. & WILSON, G. S.: Cleaning and sterilization of milk bottles, 597
HODGKISS, F.: see BROCK, R. C. *et al.*, 249
HOLIDAY, E. R.: Spectrographic examination of penicillin preparations, 228
Hormone-producing tumours of ovary, nomenclature, 360
Hormones, administration by implantation, 338, 339
— excretion after trauma, 486
— influence on physiology and pathology of ear, nose and throat, 376
Hospital infection, 553, 554, 575
— methods of control, 554, 577, 578, 579, 582, 584
— sources, 554, 575, 576, 581
HUGHES, H. P.: see DONNELLY, T. H. *et al.*, 560
HUGHES, W. & MURGATROYD, F. R.: Drug control of malaria, 310
HUNTER, J. W.: see BRANSBY, E. R. *et al.*, 537
HURFORD, J. V.: see HEAF, F. R. G. *et al.*, 336
HURST, H.: Principles of insecticidal action as a guide to drug reactivity—phase distribution relationships, 304
Hyaluronidase, production in infected tissues, 595
— in infected wounds, 592, 593, 594
Hypochlorous acid, as air disinfectant, 557, 585
Hypopyon ulcers, experimental, production and treatment, 219

I

ILAND, C. N.: Phemeride: A new antiseptic detergent, 334
Immersion foot, 395
— aetiology, 400
— experimental studies, 398
— pathology, 390, 391, 397, 398, 399, 400, 401, 402, 403, 404
— prevention, 403, 404
— treatment, 403, 404
— by low temperature, 405, 406, 407
— by sympathectomy, 412
— hand, 397, 399
Immunity and protein intake, 486
Immunology, contribution of Lister to, 550
Implantation technique of administration of non-steroid substances, 338
Inclusion bodies in association with typhus rickettsiae, 566
Industrial diseases of lungs, 243, 255
Infancy, deafness in, 377
Infants, anaemia in, blood regeneration rate in, 451, 452
— water metabolism in, 509, 510
Infection, air-borne, 553, 554
— and anaemia, 458
— communication of, in hospitals: see Hospital infection
Influenza A: outbreaks in 1943—560, 561
— virus, effect of penicillin on, 220
— B, study of 1942-43 outbreak, 558, 559
— immunization, vaccinal, 551
— bacillus: see Hamophilus influenzae
— virus, as laboratory contaminant, 562
— killing of aerial suspensions of by hypochlorous acid, 557
— laboratory studies, 559, 561, 562
— transmission, 551
ING, H. R.: Chemical constitution and pharmacological action [of drugs], 302
INGLIS, J. C.: see MCILLAN, R. B. & INGLIS, J. C., 595

INNES, J.: see DAVIDSON, L. S. P. *et al.*, 453, 454, 455, 457
 Inoculation of dangerous pathogens, apparatus for, 601
 Insecticides, phase: distribution relationships, 304
 Insulin, effect following administration by implantation, 338
 Intelligence and season of conception, 360
 Iron absorption, effect of phytic acid on, 515
 — deficiency anaemia, nutritional, 439, 440, 441, 442
 — in treatment of anaemia, 443
 — role in nutrition, 489
 — war-time supply in diet in Britain, 492
 IRWIN, J. O.: Statistical examination of the accuracy of vitamin A assays: analysis of three co-operative experiments designed to ascertain value of conversion factor for transforming spectrophotometric values into international units, 497
 Ischaemia, 413, 414, 415, 416, 417
 — pathology, 414
 — treatment, 393
 — by cooling, 389
 Iso-agglutinin titres, changes following symptomless incompatible transfusion, 436

J

JACOBY, F. C.: see WOKES, F. *et al.*, 498
 JACOBY, N. M.: Scheme for the prevention of cross-infection in children's wards, 582
 Jaundice, acholuric, inheritance and linkage relations, 437
 — following yellow-fever vaccination, 551
 JENKINS, G. N. & YUDKIN, J.: Vitamins and physiological function, 534
 JENKINS, T. I.: see ASLETT, E. A. *et al.*, 255
 JENNINGS, M. A.: see ABRAHAM, E. P., *et al.*, 212
 JENNINGS, M. A.: see CHAIN, E. *et al.*, 209
 — see FLOREY, H. W. & JENNINGS, M. A., 213
 JOHNSON, T. B., SNAGGE, J., NEGUS, V. E., FOWLER, E. P., GUTHRIE, D. & DICKSON, E. D. D.: Audibility of the radio voice [Discussion], 384
 JONES, F. A.: see YOUNG, W. F. *et al.*, 509
 JONES, H. E., ARMSTRONG, T. G., GREEN, H. F. & CHADWICK, V.: Stomatitis due to riboflavin deficiency, 533
 JONES, H. O.: see BROCK, R. C. *et al.*, 249
 JOURNALS, guide to, 291, 345, 371, 388, 419, 483, 549, 607
 JUBB, A. A.: Chemotherapy and serotherapy in cerebrospinal (meningococcal) meningitis: analysis of 3,206 case reports, 323

K

KAPPELLER-ADLER, R. & CARTWRIGHT, J. A.: Vitamin B₁ and toxemia of pregnancy, 354
 KEAY, D. M.: see COOK, R. P. *et al.*, 547
 KENNEDY, J. A.: Pulmonary complications of the common cold and sinusitis: findings in mass radiography, 277
 Kidney, failure following utero-placental damage, 356
 — function and protein intake, 486
 — in newborn infants, 509, 510
 KING, A.: see WILKINSON, P. B. & KING, A., 524
 KING, C. H.: see ANDREWES, C. H. *et al.*, 220
 KING, E. J.: see BELT, T. & KING, E. J., 254
 — see CLEGG, J. W. & KING, E. J., 469
 KING, H.: Chemical structure of arsenicals and drug resistance of trypanosomes, 303
 King, J. D.: Nutritional factors in dental caries and parodontal disease, 490
 — Mottled enamel, M-hypoplasia and dental caries, 525
 — FRANKLYN, A. B. & ALLEN, I.: Gingival disease in Gibraltar evacuee children, 530
 KLOPFER, I.: see TATE, B. C. & KLOPFER, I., 322
 KNOTT, F. A. & BLAILEY, J. B.: Control of *Staphylococcus aureus* infections in a maternity department, 584
 KNOX, R., GELL, P. G. H. & POLLOCK, M. R.: Selective action of tetrathionate in bacteriological media; report to Medical Research Council, 598
 KODICEK, E. & TRAUB, B.: Complement activity and vitamin C, 501
 KOHN, G., MILLIGAN, E. H. M. & WILKINSON, J. F.: Levels of vitamin A and C nutrition in Glossop school-children and effect of deficiency on their physical condition, 535
 KOHNSTAMM, M. L.: see MAXWELL, R. J. C. & KOHNSTAMM, M. L., 269
 KON, S. K.: see MACRAE, T. F. *et al.*, 519
 KREBS, H. A. & MELLANBY, K.: Effect of National Wheatmeal on the absorption of calcium, 512
 KYLES, W. B.: see AGNEW, A. P. & KYLES, W. B., 574

L

Lactation, effect of diet on, 364
 — nutrition during, 348, 349
 — physiology of, 366
 — premature failure of, 365, 366
 LADELL, W. S. S.: Effects of drinking small quantities of sea-water, 506
 LANGLEY, F. A. & STRATTON, F.: Haemolytic disease in the newborn: the Rh factor, 430
 LANYON, E. C. G.: see BIGELOW, W. G. & LANYON, E. C. G., 407
 Laryngectomy reed, 386
 Laryngology, development of study in Britain, 372
 LAW, W. A.: Treatment of lymphogranuloma inguinale with anthiomaline, 333
 Learmonth, J. R.: Peripheral vascular disorders, 389
 — Reflex vasodilatation in surgery, 411
 — BLACKWOOD, W. & RICHARDS, R. L.: Localised arterial thrombosis of indeterminate origin, 413
 — & RICHARDS, R. L.: Note on the spinal origin of vasoconstrictor fibres to the arm in man, 409
 — UNGLEY, C. C., BLACKWOOD, W., GAYLOR, J. B., GREENE, R. & LEWIS, T.: Discussion on immersion injuries and vasomotor disorders of the limbs in wartime, 395
 Ledingham, J. C. G.: Development of medical studies in Britain: V. Bacteriology, 550
 Leg, traumatic ischaemia, 416, 417
 LEHMANN, H.: see HALL, T. C. & LEHMANN, H., 514

Leishmaniasis, treatment with stilbamidine, 293
 LEWIS, F. J. W.: see CRAIG, A. A. *et al.*, 502
 LEWIS, T.: Swelling of human limbs in response to immersion in cold water, 396
 — see LEARMONTH, J. R. *et al.*, 395
 LEWIS-FANING, E.: Respiratory tuberculosis: effect of the war on length of interval between notification and death, 287
 LIDWELL, O. M.: see EDWARD, D. G. ff. & LIDWELL, O. M., 557
 Light, bactericidal effect on hospital ward dust, 577
 Limbs, arterial thrombosis, 413
 — immersion in cold water, effects of, 396, 397
 — injuries of, due to immersion, 395
 — vasomotor disorders, 395
 LINDSAY, S. T.: see DAVIDSON, L. S. P. *et al.*, 439, 440
 Lipidol, posture during injection of, relation to lung abscess, 249
 LIPSCOMB, J. M.: see PENFOLD, J. B. & LIPSCOMB, J. M., 465
 Lister, work of, 550, 553
 Liver disease, production in rats fed on staple African diet, 545
 — extract, in treatment of pernicious anaemia, 444, 445
 — sensitivity to, 445
 — function and protein intake, 486
 — effect of diamidines on, 316
 LLOYD, T. W.: see BAAR, H. S. & LLOYD, T. W., 451
 Lobectomy in bronchiectasis, 244
 LODGE, R. M. & HINSHELWOOD, C. N.: Some morphological and other variations in a strain of *Bact. lactis aerogenes* accompanying its adaptation to change of medium, 307
 — see SPRAY, G. H. & LODGE, R. M., 308
 LOMINSKI, I. & THOMSON, G. R.: Relative sterility of hands of certain metal workers, 603
 London, incidence of tuberculosis in, 289
 LOURIE, E. M.: Blood-brain barrier and cerebrospinal fluid in relation to efficacy of sleeping-sickness drugs, 298
 — & COLLIER, H. O. J.: Unimpaired susceptibility of *Trypanosoma rhodesiense* to arsenicals after intensive treatment by mepacrine, 314
 LOUIT, J. F., MOLLISON, M. D. & VAN DER WALT, E. D.: Venous pressure during venesection and blood transfusion, 477
 LOVELL, R.: see CLUTTERBUCK, P. W. *et al.*, 206
 Lung, abscess, 244
 — and bronchial anatomy, 247, 248
 — drainage, 250
 — relation to posture, 249
 — anatomy, 245, 246, 247, 248, 249, 250
 — cancer, sputum examination in diagnosis, 256
 — cavities, tuberculous, artificial occlusion by plasma clot, 270
 — tuberculous, closed suction drainage, 268, 269
 — persistence and closure, 265
 — cystic disease, 261
 — diseases, industrial, 243, 255
 — medical and social aspects, 243
 — see also Pneumoconiosis; Silicosis;
 Tuberculosis, pulmonary
 — interlobar fissures, 250
 — isolated, histology, 251
 — new growths, early diagnosis, 260
 — radiological picture in coal miners' pneumoconiosis, 255
 — in common cold and sinusitis, 277
 — regeneration after experimental wounds, 252
 — surgery, and bronchial anatomy, 247, 248
 — tumours, in mice and men, 253
 — wounds, experimental, healing of, 252
 LYLE, T. K., MACRAE, T. F. & GARDINER, P. A.: Corneal vascularisation in nutritional deficiency, 523
 Lymphogranuloma venereum, treatment with anthiomaline, 333
 — virus, effect of penicillin on, 220
 — morphology, 551

M

MACBETH, R. G.: see MELLANBY, E. *et al.*, 376
 MCCALL, A. J., RACE, R. R. & TAYLOR, G. L.: Rhesus antibody in Rh-positive mother causing haemolytic disease of newborn, 431
 MCCANCE, R. A., EDGEcombe, C. N. & WIDDOWSON, E. M.: Phytic acid and iron absorption, 515
 — & WIDDOWSON, E. M.: Seasonal and annual changes in the calcium metabolism of man, 511
 — & Young, W. F.: Observations on water metabolism, 488
 — Secretion of urine during dehydration and rehydration, 508
 — see BLACK, D. A. K. *et al.*, 507
 — see WIDDOWSON, E. & MCCANCE, R. A., 538
 — see YOUNG, W. F. *et al.*, 509
 MCCLEAN, D. & ROGERS, H. J.: Detection of bacterial enzymes in infected tissues, 595
 — Early diagnosis of wound infection with special reference to mixed infections, 592
 MACDONALD, A. C.: Bleeding gums and gingivitis in naval ratings, 529
 MACDONALD, N.: see CLIFFORD-JONES, E. & MACDONALD, N., 264
 MCFARLAN, A. M.: Bacteriology of brain abscess, 604
 MCFARLANE, M. N.: see RACE, R. R. *et al.*, 426
 MCILWAIN, H.: Relations between *in vivo* and *in vitro* actions of chemotherapeutic agents, 309
 MCINDOE, A. H.: see BONNEY, V. & MCINDOE, A. H., 367
 MCINTOSH, D. G.: see COOK, R. P. *et al.*, 547
 MCINTOSH, J. & SELBIE, F. R.: Chemotherapeutic drugs in anarobic infections of wounds, 216
 — Combined action of antitoxin and local chemotherapy on *Cl. welchii* infection in mice, 217
 — Zinc peroxide, proflavine and penicillin in experimental *Cl. welchii* infections, 215
 — see SELBIE, F. R. & MCINTOSH, J., 226
 MACRAE, H. M., WILLS, L., DOBBS, R. H., BINGHAM, K., FINDLAY, L., SINCLAIR, H. M., & DAVIDSON, L. S. P., YUDKIN, J. & MARSHALL, T. S.: Discussion on nutritional anaemia in children and women: a war-time problem, 442
 — see WILLS, L. *et al.*, 441
 MACKENZIE, I. F.: Nutrition and scholastic attainment, 541
 MCKEOWN, K. C.: Role of chemotherapy in treatment of haematogenous osteomyelitis, 330
 MACLEAN, I. H.: A modification of the cough plate method of diagnosis in whooping cough, 207
 — see Fleming, A. & MACLEAN, I. H., 204

MACLENNAN, J. D.: Anaerobic infections of war wounds in the Middle East, 589
 — Hyaluronidases in infected wounds, 594
 MACMAHON, J. F.: see SNELL, W. E. *et al.*, 280
 MCMICHAEL, J., SHARPEY-SCHAEFER, E. P., MOLLISON, P. L. & VAUGHAN, J. M.: Blood volume in chronic anaemia by a concentrated corpuscle-haemoglobin method, 479
 MCMILLAN, R. B. & INGLIS, J. C.: Scurvy: survey of fifty-three cases, 505
 MACNALLY, A. S.: The comprehensive attack on pulmonary tuberculosis, 286
 — Tuberculosis in peace and war, 285
 MACNAUGHTAN, J.: see CHALLINOR, S. W. & MACNAUGHTAN, J., 223
 MACPARTLAND, J. J.: see ANDERSON, P. H. R. *et al.*, 490
 MACPHERSON, A. M.: Childhood infection and its relation to adolescent and adult pulmonary tuberculosis, 282
 MACRAE, T. F., BARTON-WRIGHT, E. C. & COPPING, A. M.: Riboflavin content of food served in Royal Air Force messes, 496
 — HENRY, K. M. & KON, S. K.: Biological value of mixed proteins in food served in Royal Air Force airmen's messes, 519
 — see LYLE, T. K. *et al.*, 523
 — see PETERS, R. A. *et al.*, 493
 — see STAMM, W. P. *et al.*, 532
 MCSORLEY, J. G. & DAVIDSON, L. S. P.: Sensitivity to liver extract, 445
 — see DAVIDSON, L. S. P. *et al.*, 439, 440
 MAGASANIK, B.: see TURNER, J. C. *et al.*, 222
 MAGEE, H. E.: see BRANSBY, E. R. *et al.*, 537
 Maize, role in aetiology of liver disease among Africans, 545
 Malaria, antimalarial drugs, tests for efficacy, 312
 — avian, action of cinchona alkaloids on, 313
 — drug control, 297, 310, 311, 312, 313
 — parasite, cell metabolism in relation to mode of action of antimalarials, 297
 — therapy, mode of action of drugs in relation to plasmodium, 297
 — treatment with diamidines, 293
 MARSHALL, T. S.: see MACKAY, H. M. M. *et al.*, 442
 Mastoid infections, effect of penicillin on, 233
 MAXWELL, R. J. C. & KOHNSTAMM, M. L.: The drainage of tuberculous cavities, 269
 Maybury, B. G.: Treatment of arterial injuries, 393
 Meals, communal, 546, 547
 — in war-time Britain, 492
 Measles, immunisation, vaccinal, 551
 Meat extracts, nicotine acid and riboflavin content, 495
 Medical Research Council, and otological research, 373
 — Therapeutic Trials Committee, 292
 — WAR MEMORANDUM No. 8: Guide to the preservation of life at sea after shipwreck, 403
 Medicine in Britain, development of: II. Genetical aspect of disease, 346; III. Obstetrics, 347; IV. Oto-laryngology, 372; V. Bacteriology, 550
 MELLANBY, E.: Nutritional science in medicine, 484
 — GREENE, R. & MACBETH, R. G.: Discussion on the influence of vitamins and hormones on the physiology and pathology of the ear, nose and throat, 376
 MELLANBY, K.: see KREBS, H. A. & MELLANBY, K., 512
 MELLANBY, M. & COUMOULOS, H.: Improved definition of 5-year-old London school-children: a comparison between 1943 and 1929... 526
 MELTON, G.: Sulphamezathine in lobar pneumonia: a comparison with sulphapyridine, 326
 Ménière's disease, 381, 382, 383
 Meningitis, meningococcal, chemotherapy and serotherapy, 323
 — streptococcal, effect of penicillin on, 236
 Menstruation, anovular, and sterility, 359
 Mental defects, pulmonary tuberculosis in, 280
 Mepacrine, and arsenic-resistance, 314
 — effect of administration on electrocardiogram, 311
 — in control of malaria, 310
 — intramuscular injection, histological effect, 343
 MERLING, K. B. E.: Ultramicroscopic observations on the morphology and development of vaccinia virus *in vitro*, 565
 Metal workers, relative sterility of hands, 603
 Methionine, role in protein formation, 486
 di-Methylthiathrene, sarcocidal efficiency, 335
 MEYER, I. H.: see ALLOTT, E. N. *et al.*, 596
 Miles, A. A.: Observations on the control of hospital infection, 554
 — see GISSANE, W. *et al.*, 583
 Milk bottles, cleaning and sterilization, 597
 — war-time supply in Britain, 492
 MILLIGAN, E. H. M.: see BRANSBY, E. R. *et al.*, 537
 — see KOHN, G. *et al.*, 535
 MILLS, K. C.: see STUART-HARRIS, C. H. *et al.*, 559
 Minerals in human nutrition, 489
 — metabolism, 511, 512, 513, 514, 515
 — relation to protein, 486
 — supplementary, effect on health of girls, 536
 Miners, industrial diseases of, 243, 255
 MINISTRY OF WAR TRANSPORT: Prevention and treatment of immersion foot and of frostbite, 404
 MITCHELL, W. R. D.: see ALBERT, M. & MITCHELL, W. R. D., 417
 MITCHELL-HEGGS, G. B.: see BAKER, C. G. *et al.*, 568
 Mitigal, sarcocidal efficiency, 335
 MOIR, C. & RUSSELL, C. S.: Investigation of the effect of ergot alkaloids in promoting involution of the postpartum uterus, 350
 Molecules, physical-chemical properties, 305
 MOLLISON, M. D.: see LOUIT, J. F. *et al.*, 477
 MOLLISON, P. L.: Survival of transfused erythrocytes in haemolytic disease of the newborn, 429
 — see BOORMAN, K. E. *et al.*, 432
 — see MCMICHAEL, J. *et al.*, 479
 MONTGOMERY, G. L.: Healing of experimental wounds of lung, 252
 Morgan, W. T. J.: Chemical nature of bacterial antigens, 555
 — Occurrence and nature of human blood-group substances, 422
 MORRIS, C. J. O. R.: Determination of plasma volume by the Evans-blue method: the analysis of haemolysed plasma, 481
 Mothers, nutritional state, in industrial areas, 540
 Moulds, antibiotics from, 201

MUNRO-ASHMAN, D. & NASSAU, E.: Value of exact sputum examination (laryngeal swab culture) in diagnosis and management of pulmonary tuberculosis, 258
MURGATROYD, F.: see HUGHES, W. & MURGATROYD, F., 310
Muscular effort, effect of nicotinamide administration on, 543
— work and protein intake, 486
Mycobacterium terrae, filtration through gradocol membranes, 600
— *tuberculosis*, filtration through gradocol membranes, 600

N

Narcotics, effects on metabolic processes in central nervous system, 299
NASSAU, E.: see MUNRO-ASHMAN, D. & NASSAU, E., 258
National Collection of Type Cultures, 556
National Wheatmeal, effect on calcium absorption, 512
— vitamin B, content, 493, 494
NGUY, V. E.: see JOHNSON, T. B. *et al.*, 384
Neosarphenamine, biological standardisation, 295, 332
Nerves, peripheral, damage following immersion in cold water, 398, 399, 400, 401
— injuries of, causing vasomotor disturbances in hand, 410
— sensory, vasomotor reflexes produced by stimulation of, 408
Nervous system, central, effects of narcotics and benzedrine on metabolic processes, 299
Newborn, haemolytic disease: see Erythroblastosis foetalis
— haemorrhagic disease, 464
— fibrinogen deficiency in, 475
Nicotinamide, effect on co-ordinated muscular effort, 543
Nicotinic acid and parodontal disease, — see also Vitamin B₃
— content of beef extracts and corned beef, 495
— estimation, methods, 491
Nitrogen in potato, nutritive value, 518
NIXON, W. G. W.: Practical applications of knowledge of nutrition to pregnancy and lactation, 348
NORMAN, H. B.: Staphylococcal septicemia treated with sulphadiazine, 329
NOSÉ, influence of vitamins on, 376
Notatin, 201
Nucleoproteins, 486
Nutrition and dental caries, 490
— and war-time food policy, 484
— at home and at school, 538
— biological problems, 484
— future policy, 485
— in Britain, war-time policy, 492
— in pregnancy and lactation, 348, 349
— mineral, 489
Nutritional deficiency, 485
— in pathogenesis of disease, 544, 545
— see also Diet; Pellagra; Scurvy
— research, 485
— science in medicine, 484
— state and infection, 484
— and scholastic attainment, 541
— and size of family, 542
— effect of methods of preparation of food on, 485
— of Cambridge school-children, 539
Nyctagnus, caloric, 381
NUTT, M. E.: see GILDING, H. P. & NUTT, M. E., 473

O

O'BRIEN, J. R.: see HOARE, E. D. *et al.*, 575
O'Brien, J. R. P.: Determination of vitamins by physical, chemical and microbiological methods, 491
Obstetrics, development of study in Britain, 347
Oesophageal speech, 386
Oestrogen therapy, 368
Oil, dust-laying, value in prevention of cross-infection, 578, 579, 580
OLIVER, J. O.: see STUART-HARRIS, C. H. *et al.*, 567
ORGAN, J. G.: see WOKES, F. *et al.*, 498
ORR-EWING, J.: see CHAIN, E. *et al.*, 209
Osteomyelitis, haematogenous, chemotherapy, 330
Otolaryngology, development of study in Britain, 372
— progress of and future research in, 373
Ovarian cyst fluids, blood substances from, 422
Ovary, hormone-producing tumours, nomenclature, 369
Ovum, human, maturation and fertilization, 361
Oxford unit of penicillin potency, 239
Oxyhaemoglobin, determination of, 424

P

Pamaquine, effect of administration on electrocardiogram, 311
— in control of malaria, 310
Pantothenic acid, estimation, methods, 491
Paracolon bacillus, as inactivator of penicillin, 225
Paratyphoid-B bacillus, typing with Vi bacteriophage, 552
— carriers, detection by Vi agglutination test, 552
— fever, modern laboratory methods of control, 552
PARKES, A. S.: Administration of non-steroid substances by the implantation technique, 338
— see DEANESLY, R. & PARKES, A. S., 339
Parodontal disease, nutritional factors, 490
PARSONS-SMITH, B. G.: Tropical eosinophilia, 467
Pasteurella septica, infection of cat- and dog-bite wounds by, 596
PATERSON, E. & THOMPSON, M. V.: Effect of vitamin B on the growth of fibroblasts, 520
Pathogens, dangerous, apparatus for inoculation of animals with, 601
Patulin, 201
PAUL, J. P., HAVENS, W. P. & VAN ROOYEN, C. E.: Poliomyelitis in British and American troops in the Middle East: isolation of virus from human faeces, 564
PELLAGRA, 517
PENFOLD, J. B.: Vaccination against typhus, 569
— & LIPSCOMB, J. M.: Elliptocytosis in man associated with hereditary haemorrhagic telangiectasia, 465
Penicillamine, degradation product of penicillin, 230

Penicillin, absorption, 209, 212
— administration, intrathecal, 236
— local, 202, 233
— in therapy of war wounds, 235
— systemic, 202, 233
antibacterial action, 209, 212, 213, 214
as antiseptic snuff, 232
as therapeutic agent, 197, 209
assay, 212, 213, 224
bacteriological desiderata in treatment with, 202
bacteriostatic properties, 199
bibliography, 241, 242
broth, toxicity, 203
— use in bacteriology, 203, 204, 205, 206, 207, 208
— chemical constitution, 199
— properties, 227, 229
chemotherapeutic properties, discovery of, 199
— future prospects, 197
clinical application, 202
clinical trials, 202, 212, 232, 233, 234, 235, 236, 237, 238
discovery, 198
— effect on blood cells, 202
— on chronic wound sinuses, 233
— on *Cl. welchii*, 215, 216, 217
— on haemolytic streptococci, 234
— on healthy tissues, 226
— on influenza A virus, 220
— on lymphogranuloma venereum virus, 220
— on mastoid infections, 233
— on pneumococcus, 219
— on staphylococcus, 234
— on *Staph. aureus*, 218
— on *Strept. pyogenes*, 237
— on va cinia virus, 220
excretion, 202, 209, 212
first clinical trials, 212
in isolation of acne bacillus, 208
— of *H. pertussis*, 207
in treatment of burns, 234
— of chronic sepsis, 237
— of compound fractures, 237
— of gas gangrene, 237
— of hand infections, 202
— of head wounds, 237
— of infected bone, 202
— of infected burns, 238
— of recent soft tissue wounds, 237
— of streptococcal meningitis, 236
— of war wounds, 235, 237
inactivation, 206
— by bacterial enzyme, 210
inhibition of, in routine culture media, 225
inhibitory effect on urease, 222
morphological effects on bacteria, 211
physical and chemical properties, 199, 227
potency, *in vitro* tests of, 214
— standard of, 239
production, 206, 212, 223
— industrial, 199
properties, 197
purification, 227, 229
— methods, 199
— spectrographic examination, 228
— synergistic effect of *p*-aminobenzoic acid and sulphapyridine on, 221
— therapeutic effect, 209
toxicity, 202, 209, 212, 213
treatment with, assessment of progress, 202
— local and systemic, 197
— use for selective culture, 200
Penicillinase, 210, 225
Penicillium notatum, characteristics, 203
— cultures, antibacterial action, 203
Penicillic acid, 231
Pentamidine, in treatment of malaria infection, 293
— of trypanosomiasis, 293
— metabolic effects, 316
— pharmacological action, 315
Peripheral vessels: see Blood vessels, peripheral
PERRY, K. M. A.: see EVANS, H. & PERRY, K. M. A., 462
PETERS, R. A., CHICK, H. COWARD, K. H., HARRIS, L. J., PLATT, B. S. & MACRAE, T. F.: Vitamin B, content of national flour and bread—results of comparative tests by various methods: with appendix on thiochrome method for estimating vitamin B, in national flour and bread, 493
Pharmacodynamics, 296, 297, 298, 299, 300, 301, 302, 303, 304, 305, 306, 307, 308, 309
Phenamide (phenamidol), bactericidal value, 334
Phenamide, metabolic effects, 316
— pharmacological action, 315
PHILIPP, E.: see DONNELLY, T. H. *et al.*, 560
Phytic acid, effect on iron absorption, 515
Pitocin, oxytocic effect, 351
Pitressin, oxytocic effect, 351
Pituitary extracts, oxytocic effects, 351
— pressor effects in pregnant and non-pregnant women, 355
— relation to physiology and pathology of ear, nose and throat, 376
Pituitrin, effect of, on pregnant and non-pregnant women, 355
Placenta in eclampsia and nephritic toxemia, 357
Plasma: see Blood plasma
Plasmidium knowlesi, cell metabolism in relation to mode of action of antimetabolites, 297
Plasmoquine, effect of administration on electrocardiogram, 311
— in control of malaria, 310
Platt, B. S.: Aspects of nutritional research, 485
— & GLOCK, G. E.: Azo colour reaction for the determination of vitamin B, in national flour, 494
— see PETERS, R. A. *et al.*, 493
PLAUT, G.: see DYSON, M. & PLAUT, G., 474
POLES, F. C. & BOYCOTT, M.: Syncope in blood donors, 476
Pleura, absorption of sulphapyridine in, 321
Pneumococcus, effect of penicillin on, 219
Pneumococcosis, 243, 253, 254, 255
— in coal miners, radiological appearances, 255
Pneumectomy in bronchial carcinoma, 244
— in bronchiectasis, 244
Pneumonia, atypical, in Service personnel, 281
— chemotherapy, 324, 325
— treatment with sulphamezathine and sulphapyridine compared, 326
Pneumonolysis, internal, 263
Pneumoperitoneum in collapse therapy of lung, 264
Pneumothorax, artificial, and internal pneumonolysis, 263
— and pneumoperitoneum, 264
— and traumatic, effect of altitude on, 262
— in treatment of pulmonary tuberculosis, 244

Poliomyelitis, experimental work on, in Egypt, 563
— in British and American troops in the Middle East, 564
— virus, isolation from human faeces, 564
— transmission, 551
POLLOCK, M. R.: see KNOX, R. *et al.*, 598
Posture during injection of iodised oil, relation to lung abscess, 249
Potassium tellurite, antibacterial properties, 205
Potato, nitrogenous substances, nutritive value, 518
POWELL, E. O.: see BROWN, G. M. *et al.*, 450
POWNEY, J.: see HARWOOD, F. G. *et al.*, 579
Pregnancy, anaemia in, megaloblastic, 457
— anaemias of, haematological study of 48 cases, 456
— of, recent work on, 423
— nutrition in, 348, 349
— toxemia in, aetiology, 354
— placenta in, 357
— vitamin-C level in, in war-time, 502
PRESCOTT, F.: see CLARKE, A. G. & PRESCOTT, F., 516
Proflavine, as antiseptic snuff, 232
— local antiseptic action, 340
— powder, histological effect on fresh wounds, 341, 342
Promin, in treatment of pulmonary tuberculosis, 336
Propamidine, in treatment of burns, 234
— of trypanosomiasis, 293
— metabolic effects, 316
— pharmacological action, 315
Propylene glycol, as air disinfectant, 587, 588
Protein, deposition in implanted steroid hormones, 339
— hydrolysates, therapeutic effects, 486
— intake, increased, effect on calcium absorption, 514
— metabolism, 486
— mixed, biological value, 519
— relation to mineral metabolism, 486
— relation to trauma and wound-healing, 486
— requirements, 486
— transmutation, 486
— war-time supply in Britain, 492
Proteus vulgaris, as inactivator of penicillin, 225
Prothrombin index in haemorrhagic disease of newborn, 464
FRUNTY, F. T. G. & VASS, C. C. N.: Assessment of vitamin-C nutrition in man, 503
— Vitamin-C nutrition in a hospital: with observations on a case of scurvy, 504
Pseudomonas pyocyanea, as inactivator of penicillin, 225
— in sputum, biochemical classification of, 605
Pseudo-mucinous ovarian cyst fluid, blood substances from, 422
Psittacosis virus, morphology, 551
PULVERTAFT, R. J. V.: Bacteriology of war wounds, 590
— Local therapy of war wounds: I. With penicillin, 235
— Use of antiseptic sprays for air sterilization: summary of report to Medical Research Council, 585
Purpura, thrombocytopenic, 462
PYKE, M.: Some principles of war-time food policy, 492
Pyridine-haemochromogen, determination of, 424
Pyridoxine, estimation, methods, 491

Q

QUASTEL, J. H.: Effects of narcotics and benzedrine on metabolic processes in the central nervous system, 299
Quinacrine: see Mepacrine
Quinoline derivatives: comparison of action of Bayer 7602 (Ac) with corresponding I.C.I. product, 317

R

Rabies, vaccination as prophylaxis, 551
RACE, R. R.: Some recent observations on the inheritance of blood groups, 421
— An 'incomplete' antibody in human serum, 435
— Inheritance and linkage relations of acholuric jaundice, 437
— TAYLOR, G. L., CAPPELL, D. F. & McFARLANE, M. N.: Rh factor and erythroblastosis foetalis: an investigation of 50 families, 426
— see McCALL, A. J. *et al.*, 431
— see TAYLOR, G. L. & RACE, R. R., 420, 433
RACKOW, A. M.: see CLELAND, W. P. & RACKOW, A. M., 278
Radiography, mass, 243
— in women, 279
Radiology and thoracic surgery, 244
— in post-operative chest surgery, 278
RAISTRICK, H.: see CLUTTERBUCK, P. W. *et al.*, 206
Raspberry leaves, oxytocic effect, 353
Reflex, aural, 381, 382
Rehabilitation in chest diseases, 276
— of tuberculous patient, 243
Reproduction, effect of diet on, 364
Resorcinol, effect on growth of *Bact. lactis aerogenes*, 308
Respiratory infection, value of oiled floors in control of, 580
RETTIE, G. K. C.: see STUART-HARRIS, C. H. *et al.*, 567
Rh factor, 429
— and erythroblastosis foetalis, 426, 427, 428, 429, 430, 431, 432, 433
— incidence in the population, 428
— sub-types, 420
— terminology, 420
— see also Blood-group substances
Rh-positive fathers, haemorrhagic, preponderance in haemolytic disease of newborn, 433
Riboflavin content of beef extracts and corned beef, 495
— of food served to R.A.F., 496
— deficiency, 517
— ocular manifestations, 517, 522
— relation to stomatitis, 533
— estimation, methods, 491
RICHARDS, M. B.: Dietary factor in reproduction and lactation, 364
RICHARDS, R. L.: Injury from exposure to low temperature: clinical features, prevention, treatment, 392
— Vasomotor disturbances in the hand after injuries of peripheral nerves, 410
— see LEARMONTH, J. R. & RICHARDS, R. L., 409
— see LEARMONTH, J. R. *et al.*, 413

RICHTER, D. & CROFT, P. G.: Estimation of 'true ascorbic acid' in blood, 500
 — Estimation of "true" ascorbic acid in urine, 499
 Rickettsiae, apparatus for safe inoculation of, 601
 — see also Typhus
 RIDEAL, E. K.: Physico-chemical aspects [of drug action], 301
 RIDING, D.: see DAVIS, L. J. et al., 444
 ROBERTS, J. A. F.: Intelligence and season of conception, 360
 ROBERTS, J. C.: Tuberculosis in children, 283
 ROBERTSON, D.: see DONNELLY, T. H. et al., 560
 ROBINSON, M.: Failing lactation, 365
 ROBINSON, R.: see ABRAHAM, E. P. et al., 230
 ROBSON, J. M. & SCOTT, G. I.: Local chemotherapy in experimental lesions of the eye produced by *Staphylococcus aureus*, 218
 — Production and treatment of experimental pneumococcal hypopyon ulcers in the rabbit, 219
 RODGERS, T. S.: see BRANSBY, E. R. et al., 537
 ROGERS, H. J.: see McCLEAN, D. & ROGERS, H. J., 592, 595
 RUSSELL, C. S.: Response of isolated muscle-strips from upper and lower segments of the human full-time pregnant uterus to pitressin and pitocin, 351
 — see MOIR, C. & RUSSELL, C. S., 350
 RUSSELL, D. S. & BECK, D. J. K.: Histological effects of sulphonamide-proflavine mixtures in the rabbit: experimental observations, 342
 — & FALCONER, M. A.: Acridine antiseptics: further experiments on their local action, 340
 RUSSELL, H.: see BLACKWOOD, W. & RUSSELL, H., 398

S

SAIFT, M. F. & VAUGHAN, J. M.: Anaemia associated with infection, 458
 St. John-Brooks, R.: National Collection of Type Cultures, 556
 Saliva, blood-group substances from, 422
 SALM, R.: Biochemical classification of coliform bacilli in sputum, 605
 Salpingitis and sterility, 359
 Salt balance and water intake, 488
 — water, effect of drinking, 506
 SAMUEL, E.: see DREW, W. R. M. et al., 281
 SANDERS, A. G.: see CHAIN, E. et al., 209
 Scabies, therapy, 335
 Scarborough, H.: Clinical haemoglobinometry, 424
 Scholar, attainment in relation to nutritional state, 541
 SCHULMAN, J. H.: Some physical-chemical properties of biologically active molecules, 305
 SCOBIE, E. B. S.: Haemorrhagic disease of the newborn, 464
 SCOTCHER, N. M.: see WIEN, R. et al., 316
 SCOTT, G. I.: see ROBSON, J. M. & SCOTT, G. I., 218, 219
 Scurvy, ascorbic acid concentration in, 504, 505
 — survey of 53 cases, 505
 — treatment, present knowledge, 487
 Sea-water, effect of drinking, 506
 Semen, intramuscular injection, effect on uterus, 358
 SELBIE, F. R. & MCINTOSH, J.: Action of chemotherapeutic drugs (including proflavine) and excipients on healthy tissue, 226
 — see MCINTOSH, J. & SELBIE, F. R., 215, 216, 217
 SELLORS, T. H.: Closed suction drainage of tuberculous cavities, 268
 Sepsis, chronic, treatment with penicillin, 237
 Septicæmia, staphylococcal, treatment with sulphadiazine, 329
 Serum, anti-meningococcal, evaluation of, 323
 — human, bacteriostatic power, measurement of, 240
 — incomplete antibody in, 435
 SHAPIRO, B. G.: see HEIMANN, H. L. & SHAPIRO, B. G., 311
 SHARMAN, A.: Some recent studies and investigations in sterility, 359
 Sharpey-Schafer, E. P.: Circulatory dynamics of haemorrhage, 425
 — see McMICAL, J. et al., 479
 SHAW, G. E.: see DAVIS, L. J. et al., 444
 Shipwreck, preservation of life at sea after, 403
 SHOOTER, R. A. & WATERWORTH, P. M.: Note on transmissibility of hæmolytic streptococcal infection by flies, 581
 Silicosis, 243
 — experimental, failure of aluminium in prevention of, 254
 SINCLAIR, H. M.: see MACKAY, H. M. M. et al., 442
 Sinusitis, pulmonary complications, 277
 SIPPE, G. R.: Autolysed yeast in treatment of nutritional macrocytic anemia, 446
 Skin, immersion in cold water, effects of, 396
 Skull, abnormality, in infancy, 362, 363
 Slide-cell technique for measurement of bacteriostatic power of blood and serum, 240
 Smallpox, treatment with sulphanilamide, 331
 SMART, G. A.: Incidence of gingivitis in the Royal Air Force, 531
 SMITH, H. G.: Sulphaguanidine in the treatment of Flexner dysentery, 328
 SMITH, S.: see DUFFIN, W. M. & SMITH, S., 231
 SMITH, W. & HALE, J. H.: Nature and mode of action of staphylococcus coagulase, 602
 — & WILSON, A.: Effect on the uterus of extracts of gorse (*Ulex gallii*), 352
 — see ANDREWES, C. H. et al., 562
 SNAGGE, J.: see JOHNSON, T. B. et al., 384
 SNELL, W. E., MACMAHON, J. F. & HEAF, F. R. G.: Tuberculosis survey at a mental hospital by miniature radiography, 280
 Snuffs, antiseptic, 232
 Sodium hypochlorite, as air disinfectant, 557, 585
 SOLTYS, M. A. & TAYLOR, A. W.: The filtration of *Mycobacterium tuberculosis* and *Mycobacterium stercuris* through gradocol membranes, 600
 Speech, audibility, 384
 — defects, 385, 386
 — therapy, 386
 — therapy, scope of, 374
 Splenectomy in thrombocytopenic purpura, 462
 SPRAY, G. H. & LODGE, R. M.: The effects of resorcinol and of *m*-cresol on the growth of *Bact. lactis aerogenes*, 308
 Sputum, coliform bacilli in, biochemical classification of, 605
 — examination in diagnosis of lung cancer, 256
 — value in diagnosis of pulmonary tuberculosis, 257, 258

St serum, 420
 — discovery of, 431
 STAMM, W. P., MACRAE, T. F. & YUDKIN, S.: Incidence of bleeding gums among R.A.F. personnel and the value of ascorbic acid in treatment, 532
 STANFORD, S.: Traumatic ischæmia in the forearm and leg, 416
 STANNUS, H. S.: Some problems in riboflavin and allied deficiencies, 517
 STANSFELD, J. M. & STUART-HARRIS, C. H.: Clinical study of an outbreak of influenza B during the winter 1942-43...558
 Staphylococcus coagulase, nature and mode of action, 602
 — effect of penicillin on, 234
 — septicæmia, treatment with sulphadiazine, 329
Staphylococcus aureus, effect of penicillin on, 218
 — in maternity hospital, control of, 584
 Sterility in the male, 358
 — investigation and treatment, new developments, 358, 359
 — psychological aspects, 358
 Sternal puncture findings in refractory anemias, 453, 454, 455
 Steroid hormones, administration by implantation, 339
 STEWART, C. P.: Some problems of communal feeding, 546
 Stilbamidine, in treatment of malaria infection, 293
 — in treatment of trypanosomiasis, 293
 — metabolic effects, 316
 — pharmacological action, 315
 STILL, B. M.: see THOMAS, D. et al., 270
 Stomatitis, due to riboflavin deficiency, 533
 STRAKER, E.: see ALLOTT, E. N. et al., 596
 — see DELAFIELD, M. E. et al., 232
 STRATTON, F.: see LANGLEY, F. A. & STRATTON, F., 430
 Streptococci, hæmolytic, effect of penicillin on, 234
 — in dust of hospital wards: relationship to infection, 576, 577, 578
 — production of hyaluronidase by, 592, 593, 594
 — transmission by flies, 581
Streptococcus pyogenes, effect of penicillin on, 237
 STUART-HARRIS, C. H., GLOVER, R. E. & MILLS, K. C.: Influenza in Britain, 1942-43...559
 — RUTTIE, G. K. C. & OLIVER, J. O.: Rickettsial agglutination studies in typhus fever, 567
 — see STANSFELD, J. M. & STUART-HARRIS, C. H., 558
 Sulfanyl sulphathiazole, pharmacology, 294
 SUGGILL, S.: Deafness resulting from gunfire and explosions, 380
 Sulphadiazine in treatment of staphylococcal septicæmia, 329
 Sulphaguanidine in treatment of Flexner dysentery, 328
 — in treatment of neonatal epidemic gastroenteritis, 327
 Sulphamerazine, pharmacology, 294
 Sulphamezathine, in treatment of lobar pneumonia, 326
 — pharmacology, 294
 Sulphanilamide, distribution in body fluids and tissues, 319
 — effect on acid-base balance, 294
 — in treatment of lymphogranuloma inguinale, 333
 — in treatment of smallpox, 331
 Sulphapyrazine, pharmacology, 294
 Sulphapyridine, absorption and excretion, effect of acid, alkali and meals on, 320
 — through human pleura, 321
 — in treatment of pneumonia, 324, 325, 326
 — synergistic effect on penicillin, 221
 Sulphasphenamine, biological standardisation, 332
 Sulphasuxidine, pharmacology, 294
 Sulphathiazole as antiseptic snuff, 232
 — in anaerobic infections, comparison with penicillin, 216
 — in treatment of hæmatogenous osteomyelitis, 330
 — powder, histological effect on wounds, 342
 Sulphonamide-proflavine powder, histological effect on wounds, 342
 Sulphonamides, absorption rate, 294
 — action in relation to diet, 294
 — on various organs, 294
 — blood-concentrations, 294
 — combination with plasma proteins, 294
 — distribution, 294
 — effect on growth of *Bact. lactis aerogenes*, 309
 — estimation of, in body fluids, 294
 — excretion mechanism, 294
 — in treatment of meningococcal meningitis, evaluation of, 323
 — local, action, 318
 — sensitisation to, 322
 — toxic reactions to, 322
 — metabolism, 294
 — pharmacology, recent work, 294
 — relations between *in vivo* and *in vitro* actions, 300
 Sympathectomy, for modification of peripheral circulation, 389
 — in treatment of injuries due to cold, 412
 Syncope in blood donors, 476, 478
 Synthalin, action, 293

T

TATE, B. C. & KLOFAJN, I.: Sulphonamide dermatitis: sensitisation from local application, 322
 TAYLOR, A. W.: see SOLTYS, M. A. & TAYLOR, A. W., 600
 Taylor, G. L. & Race, R. R.: Human blood groups, 420
 — Hæmolytic disease of the newborn: the preponderance of homozygous Rh-positive factors, 433
 — see MCCALL, A. J. et al., 431
 — see RACE, R. R. et al., 426
 TEE, G.: see ALLOTT, E. N. et al., 596
 Teeth and nutrition, 490
 — diseases, nutritional factors, 525, 526, 527, 528
 — enamel, mottling and M-hypoplasia, effect of fluorine on, 525, 526, 527, 528
 Telangiectasia, hæmorrhagic, hereditary, and elliptocytosis, 465
 TELFORD, E. D.: Sympathectomy in treatment of the cryopathies, 412
 Temperature, low, injury from exposure to (pathology, clinical features, prevention, treatment), 390, 391, 392
 Testicular biopsy, in investigation of sterility, 358

Tetmos, sarcocidal efficiency, 335
 Tetra-ethylthiuram monosulphide, sarcocidal efficiency, 335
 Tetrathionate, in bacteriological media, selective action, 598
 Therapeutic Trials Committee, function of, 292
 THOMAS, C. P.: Pulmonary cavities: their persistence and closure, 265
 — Thoracic injuries: rôle of the general surgeon in the forward area, 272
 — & CLELAND, W. P.: Ektrafascial apicolysis with thoracoplasty, 266
 — Results of thoracoplasty, 267
 THOMAS, D., GOUGH, J. & STILL, B. M.: Artificial bronchial occlusion by plasma clot in treatment of chronic tuberculous cavitation, 270
 THOMAS, P. E.: see BARANGER, P. & THOMAS, P. E., 313
 THOMPSON, B. C.: Survival rates in pulmonary tuberculosis, 288
 THOMPSON, M. V.: see PATERSON, E. & THOMPSON, M. V., 520
 THOMSON, G. R.: see LOMINSKI, I. & THOMSON, G. R., 603
 THOMSON, M. L.: see CLARK, A. M. et al., 234
 Thoracic surgery, present position, 244
 — in wartime, 271, 272, 273, 274
 — scope of, 275
 Thoracoplasty, and ektrafascial apicolysis, 266
 — in pulmonary tuberculosis, 244
 — results, 267
 Thorax, injuries, closed, pathology of, 273
 — war wounds and injuries, 271, 272
 Throat, influence of vitamins on, 376
 Thrombocytosis, experimental, blood platelets in, 463
 Thyroxine, effect following administration by implantation, 338
 TODD, G. S. & ANDERSON, D. M.: Effect of altitude on cases of pneumothorax, 262
 Tonephin, effect of on pregnant and non-pregnant women, 355
 TONKS, E.: see HICKMANS, E. M., FINCH, E. & TONKS, E., 471
 TOPLEY, W. W. C.: see DELAFIELD, M. E. et al., 232
 TRAUB, B.: see KODICK, E. & TRAUB, B., 501
 TROWELL, O. A.: Histology of the isolated perfused lung, 251
 Trypanocides, efficacy of various routes of administration, 337
 — non-arsenical, pharmacological action of, 315
Trypanosoma rhodesense, susceptibility to arsenicals following mepacrine treatment, 314
 Trypanosomes, resistance to drugs, 303
 Trypanosomiasis, comparative efficacy of Bayer 7602 (Ac) and corresponding I.C.I. product, 317
 — therapy, blood-brain barrier and cerebrospinal fluid in relation to efficacy of trypanocides, 298
 — treatment with diamidines, 293
 TUBBS, O. S.: Scope of modern chest surgery, 275
 Tubercle bacillus, filtration through gradocol membranes, 600
 Tuberculosis, medical and social aspects, 243
 — pulmonary, at a mental hospital, 280
 — diagnosis, value of sputum and gastric juice examination in, 257, 258
 — effect of war on length of interval between notification and death, 287
 — in children, 282, 283, 284
 — in peace and war, 285, 287, 289
 — incidence in London, 289
 — social and statistical aspects, 285, 286, 287, 288, 289
 — surgical treatment, 244, 265, 266, 267, 268, 269, 270
 — survival rates, 288
 — treatment with promin, 336
 TUNBRIDGE, R. E.: see WILSON, J. V. & TUNBRIDGE, R. E., 274
 TURNER, J. C., HEATH, F. K. & MAGASANK, B.: Inhibition of urease by penicillin, 222
 TWORT, C. C.: see BAKER, A. H. & TWORT, C. C., 586
 TYAGI, N.: see BARDHAN, P. N. et al., 571
 Typhoid bacillus, typing by Vi bacteriophage, 552
 — carriers, detection by Vi agglutination test, 552
 Typhoid fever, modern laboratory methods of control, 552
 Typhus, diagnosis by dry blood test, 571
 — preparation of suspensions for Weil-Felix test, 573
 — technique and interpretation of Weil-Felix test, 572
 — endemic, in Madagascar, 568
 — in Gt. Britain, 574
 — in Middle East, 570
 — rickettsiae, agglutination studies, 567
 — inclusion bodies in association with, 566
 — vaccination against, 569
 Tyrocidine, 201

U

UNGAR, J.: Synergistic effect of para-aminobenzoic acid and sulphapyridine on penicillin, 221
 UNGLEY, C. C.: Immersion foot and immersion hand (peripheral vasoneuropathy after chilling), 399
 — Treatment of immersion foot by dry cooling, 406
 — & BLACKWOOD, W.: Peripheral vasoneuropathy after chilling: "Immersion foot and immersion hand," 397
 — see LEARMONTH, J. R. et al., 395
 UNSWORTH, K.: see GORDON, R. M. & UNSWORTH, K., 335
 Urease, inhibition of by penicillin, 222
 Urine, blood-group substances from, 422
 — estimation of ascorbic acid in, 499
 — secretion during dehydration and rehydration, 508
 Utero-placental damage and renal failure, 356
 Uterus, effect of gorse extracts on, 352
 — endometrium, tuberculosis, 359
 — postpartum, involution with ergot alkaloids, 350
 — pregnant, effect of pituitary extracts on, 351
 — effect of raspberry leaves on, 353

V

Vaccines, in prophylaxis of virus diseases, 551
 Vaccinia virus, effect of penicillin on, 220
 — morphology and development *in vitro*, 565
 — ultramicroscopical observations, 565
 Vagina, artificial, construction, 367

VAN DEN ENDE, M.: Apparatus for the safe inoculation of animals with dangerous pathogens, 601
 — see ANDREWS, C. H. et al., 220
 — see BEGG, A. M. et al., 566
 VAN DER WALD, E. D.: see LOUIT, J. F. et al., 477
 VAN ROOYEN, C. E. & MORGAN, A. D.: Poliomyelitis: experimental work in Egypt, 563
 — see PAUL, J. R. et al., 564
 Vasoconstrictor fibres, spinal origin of, 409
 Vasodilatation, reflex, in surgery, 411
 Vasomotor disturbances in hand after injuries of peripheral nerves, 410
 — reflexes, mechanism of production by stimulation of sensory nerves, 408
 — responses of hand following section of anterior nerve roots, 409
 VASS, C. C. N.: see PRUNTY, F. T. G. & VASS, C. C. N., 504
 VAUGHAN, J. M.: see McMICHAEL, J. et al., 479
 — see SAIT, M. F. & VAUGHAN, J. M., 458
 Vegetables, war-time supply in Britain, 492
 Veins, blood-pressure in, during venesection and blood transfusion, 477
 — following haemorrhage, 425
 — thrombosis, traumatic, 395
 Vestibular function, 381, 382, 383
 Vi agglutination test, use in detection of typhoid and paratyphoid-B carriers, 552
 — bacteriophage, in typing of typhoid and paratyphoid-B bacillus, 552
 VICKERS, H. E.: Sulphapyridine absorption through the human pleura, 321
 Virus diseases of man: review of recent progress, 551
 — chemotherapy, 551
 Viruses, agglutination of erythrocytes by, 551
 — apparatus for safe inoculation of, 601
 — chemical and physical studies, 551
 — classification, 551
 — culture, 551
 — interference phenomenon, 551
 Vitamin A and parodontal disease, 490
 — deficiency, effect on ear, 376
 — estimation, methods, 491
 — levels in school-children, 535
 — standardization, statistical examination of accuracy of methods, 497
 — war-time supply in Britain, 492
 — B deficiency, mental and oral manifestations, 516
 — determination, methods, 491
 — effect on growth of fibroblasts, 520
 — B, and toxæmia of pregnancy, 354
 — estimation, in national flour and bread, 493, 494
 — war-time supply in Britain, 492
 — B₂: see Nicotinic acid: Riboflavin
 C, and parodontal disease, 490
 — apparent increase in stored food, 498
 — effect on upper respiratory tract infections, 376
 — estimation in blood, 500
 — in urine, 499
 — methods, 491
 — evaluation of present knowledge of, 487
 — in treatment of anaemia, 443
 — intake, and complement activity, 501
 — level in pregnancy in war-time, 502
 — in scurvy, 504, 505
 — levels in school-children, 535
 — nutrition in hospital residents, 503, 504
 — relationship to calcification of bone, 521
 — requirements, assessment of, 487
 — saturation, 487
 — value in treatment of bleeding gums, 532
 — war-time supply in Britain, 492
 — D, and calcium metabolism, 489
 — estimation, methods, 491
 — war-time supply in Britain, 492

Vitamin K, in treatment of hæmorrhage disease of newborn, 464
 Vitamins, deficiency, effect on physical condition of school-children, 535
 — determination, physical, chemical, and microbiological methods, 491
 — effect on physical fitness, 534, 535, 536, 537, 538, 539, 540, 541, 542, 543
 — estimation, in food and body-fluids, 493, 494, 495, 496, 497, 498, 499, 500
 — influence on physiology and pathology of ear, nose and throat, 376
 — supplementary, effect on physical condition, 534, 535, 536, 537, 539, 543
 Voice, audibility, 384
 — see also Speech
 — disorders, speech therapy in, 374, 386
 Volkmann's ischæmic contracture, 415, 417

W

WALKER, K.: see GREEN-ARMYtage, V. B. et al., 358
 WALLER, H. K.: Reflex governing the outflow of milk from the breast, 366
 WARDLEY, J. R.: see GORDON, C. M. & WARDLEY, J. R., 472
 War-time, occurrence of anaemia in, 439, 440, 441, 442
 Water and salt balance in man, 488
 — effect of reduced intake, 488, 507, 508
 — metabolism, 488, 506, 507, 508, 509, 510
 — in infants, 509, 510
 — sources of intake in man, 488
 WATERWORTH, P. M.: see SHOOTER, R. A. & WATERWORTH, P. M., 581
 WATKINS, A. G.: see HOARE, E. D. et al., 575
 WATSON, L.: Red-cell suspension transfusions, 460
 WEAVER, R.: Fluorosis and dental caries on Tyne-side, 527
 — Fluorine and dental caries: further investigations on Tyneside and in Sunderland, 528
 WEIGERT, F.: A possible mode of action of benzpyrene as a typical chemical carcinogen, 306
 Weil-Felix test, preparation of suspensions for, 573
 — technique and interpretation, 572
 WEINGARTEN, R. J.: Tropical eosinophilia, 466
 WHITTAKER, S. R. F.: see BROCKBANK, W. & WHITTAKER, S. R. F., 570
 Whooping cough, diagnosis, 207
 WIDDOWSON, E. M.: Minerals in human nutrition, 489
 — & McCANCE, R. A.: Growth at home and at school, 538
 — see McCANCE, R. A. & WIDDOWSON, E. M., 511
 — see McCANCE, R. A. et al., 515
 WIEN, R.: Pharmacological actions of certain aromatic diamidines possessing trypanocidal activity, 315
 — FREEMAN, W. & SCOTCHER, N. M.: Metabolic effects produced by certain aromatic diamidines, 316
 WILKINSON, J. F.: see KOHN, G. et al., 535
 WILKINSON, P. B.: Sulphanilamide in the treatment of smallpox, 331
 — & KING, A.: Amblyopia due to a vitamin deficiency, 524
 WILLIAMS, R. E. O.: see GISSANE, W. et al., 583
 WILLIS, F. E. S. & ALMEYDA, J.: Cystic disease of the lung (broncho-alveolar cysts), 261
 WILLS, L. MACKAY, H. M., BINGHAM, K. & DOBBS, R. H.: Anaemia in women and children on war-time diets, 441
 — see MACKAY, H. M. et al., 442
 WITTS, L. J.: see BROWN, G. M. et al., 450
 WILSON, A.: see SMITH, W. & WILSON, A., 352
 WILSON, G. S.: see HOBBS, B. C. & WILSON, G. S., 597

WILSON, H. E. C.: Effect of acid, alkali, and meals on the blood level and excretion of sulphapyridine in children, 320
 WILSON, J. V.: The pathology of closed injuries of the chest, 273
 — & TUNBRIDGE, R. E.: Pathological findings in a series of blast injuries, 274
 WILSON, U.: New rapid method for penicillin assay, 224
 WITHELL, E. R.: see BURN, J. H. & WITHELL, E. R., 353
 WITTKOWER, E. W.: see GREEN-ARMYtage, V. B. et al., 358
 WOKES, F., ORGAN, J. G., DUNCAN, J. & JACOBY, F. C.: Apparent vitamin C in foods, 498
 Women, anaemia in, due to war-time diet, 441, 442
 — mass radiography findings, 279
 WOODMAN, D.: see CRAIG, A. A. et al., 502
 Wound-healing, role of protein and amino-acids in, 486
 Wounds, dressing-technique, 554, 583
 — effect of powdered proflavine on, 341, 342
 — effect of sulphonamides applied locally, 318
 — infected, effect of penicillin on, 238
 — production of hyaluronidase in, 592, 593, 594
 — infection, anaerobic, 589
 — effect of penicillin on, 216
 — bacteriology, 590, 591
 — clinical investigation, 591
 — early diagnosis, 592
 — in hospital, 553, 583
 — with *P. septicæ*, 596
 — sinuses, chronic, effect of penicillin on, 233
 — war, effect of penicillin on, 235, 237
 WRIGHT, H. A.: Laboratory diagnosis of diphtheria: note on some present-day methods, 599
 WRIGHT, H. P.: Sources of blood platelets and their adhesiveness in experimental thrombocytosis, 463
 WRIGHT, J., CRUICKSHANK, R. & GUNN, W.: Control of dust-borne streptococcal infection in measles wards, 578

Y

Yeast, autolyzed, in treatment of macrocytic anaemia, 446
 Yellow fever vaccination and jaundice, 551
 Yorke, W.: Therapeutic action of the aromatic diamidines in the treatment of protozoal infections of man and stock, 293
 — see FULTON, J. D. & YORKE, W., 337
 Young, J.: Development of medical studies in Britain. III. Obstetrics, 347
 YOUNG, J.: Renal failure after utero-placental damage, 356
 YOUNG, W. F., McCANCE, R. A., JONES, F. A. & DOBBS, R.: Discussion on water metabolism in sick and healthy infants, 509
 — see BLACK, D. A. K. et al., 507
 — see McCANCE, R. A. & YOUNG, W. F., 488, 508
 YUDKIN, J.: Relative efficacy of calcium carbonate and calcium phosphate in preventing rickets in rats, 513
 — Nutrition and size of family, 542
 — Nutritional deficiency in the pathogenesis of disease, 544
 — Nutritional status of Cambridge school-children, 539
 — Nutritional status of children and mothers of industrial towns, 540
 — see JENKINS, G. N. & YUDKIN, J., 534
 — see MACKAY, H. M. et al., 442
 YUDKIN, S.: see STAMM, W. P. et al., 532

Z

ZILVA, S. S.: Evaluation of the vitamin-C position, 487

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 KENNEDY, J. A.: see TRAIL, R. R., TRENCHARD, H. G. & KENNEDY, J. A., 290/1
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- McMURRAY, T. P.: *Practice of orthopaedic surgery*, 2nd ed., 344/21
- McNEE, J. W.: *see* DUNLOP, D. M. *et al.*, 387/34
- McNEIL, C.: *see* KERR, J. M. M. *et al.*, 387/45
- MANCHÉ, D.: *Social service in a general hospital*, 418/63
- MARSHALL, J.: *The venereal diseases: a manual for practitioners and students*, 606/95
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- WAR MEMORANDUM No. 10: *Medical use of sulphonamides*, 344/9
- WAR MEMORANDUM No. 11: *Control of cross infection in hospitals*, 387/39
- WAR MEMORANDUM No. 12: *Use of penicillin in treating war wounds*, 387/51
- MEGAW, J. D. W.: *see* ROGERS, L. & MEGAW, J. D. W., 606/104
- MERCER, W.: *Orthopaedic surgery*, 3rd ed., 344/19
- MINISTRIES OF HEALTH & WORKS: *Housing manual*, 548/87
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- MINISTRY OF HEALTH AND DEPT. OF HEALTH FOR SCOTLAND: *Report of Inter-departmental Committee on Medical Schools*, 482/73
- MINNITT, R. J.: *Gas and air analgesia*, 418/55
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- MOLESWORTH, H. W. L.: *Regional analgesia*, 482/72
- MONCRIEFF, A. A.: *see* ROLLESTON, SIR H. & MONCRIEFF, A. A., 482/68, 548/85
- MUSHIN, W. W.: *see* MACINTOSH, R. R. & MUSHIN, W. W., 606/96
- NATIONAL COUNCIL FOR MATERNITY AND CHILD WELFARE: *The training of the nursery nurse*, 482/78
- NEAME, H. & WILLIAMSON-NOBLE, F. A.: *Handbook of ophthalmology*, 5th ed., 344/24
- OGILVIE, R. F.: *Pathological histology*, 2nd ed., 344/10
- OGILVIE, W. H.: *Forward surgery in modern war*, 418/59
- PARFITT, J. B. & HERBERT, W. E.: *Operative dental surgery*, 5th ed., 482/66
- PARKER, G. E.: *The surgery of abdominal trauma*, 482/80
- PLESCH, J.: *The blood pressure and its disorders including angina pectoris*, 418/64
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- ROGERS, L. & MEGAW, J. D. W.: *Tropical medicine*, 5th ed., 606/104
- ROLLESTON, SIR H. & MONCRIEFF, A. A.: *Industrial medicine*, 482/68
- ROXBURGH, A. C.: *Common skin diseases*, 7th ed., 482/74
- ROYAL COLLEGE OF OBSTETRICIANS AND GYNÆCOLOGISTS: *Report on a national maternity service*, 387/43
- ROYAL COLLEGE OF PHYSICIANS: *Report on medical education*, 387/52
- ROYAL COLLEGE OF SURGEONS OF ENGLAND: *General annual report of the Council*, 1944, 606/101
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- SARGANT, W. & SLATER, E.: *Introduction to physical methods of treatment in psychiatry*, 548/86
- SCOTLAND, DEPT. OF HEALTH: *Sulphonamides in the treatment of meningococcal meningitis*, 548/83
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- SHELDON, W.: *Diseases of infancy and childhood*, 4th ed., 344/11
- SLATER, E.: *see* SARGANT, W. & SLATER, E., 548/86
- TRAIL, R. R.: *Chest examination: correlation of physical and x-ray findings in disease of the lungs*, 290/2
- TRENCHARD, H. G. & KENNEDY, J. A.: *Mass miniature radiography*, 290/1
- TREDGOLD, A. F.: *Manual of psychological medicine: for practitioners and students*, 387/37
- TRENCHARD, H. G.: *see* TRAIL, R. R., TRENCHARD, H. G. & KENNEDY, J. A., 290/1
- WALSHE, F. M. R.: *Diseases of the nervous system*, 3rd ed., 344/12
- WATSON-JONES, R.: *Fractures and joint injuries*, 3rd ed., 290/7
- WHITBY, L. E. H.: *Medical bacteriology*, 4th ed., 344/20
- WHITE, M. M.: *The symptomatic diagnosis and treatment of gynaecological disorders*, 387/38
- WILLIAMSON-NOBLE, F. A.: *see* NEAME, H. & WILLIAMSON-NOBLE, F. A., 344/24
- WILSON, G. J.: *see* KERR, J. M. M. *et al.*, 387/45
- WORTH, C.: *see* MAY, C. H. & WORTH, C., 606/92
- WYBURN-MASON, R.: *The vascular abnormalities and tumours of the spinal cord and its membranes*, 370/28
- YOUNG, J.: *Text-book of gynaecology for students and practitioners*, 6th ed., 606/100
- *see* KERR, J. M. M. *et al.*, 387/45
- YOUNG, J. H.: *Cæsarean section: the history and development of the operation from earliest times*, 370/26
- ZIEVE, I. E.: *Aids to orthopaedic surgery and fractures*, 2nd ed., 606/103

BRITISH MEDICAL BULLETIN

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No. 1

PENICILLIN 1929-1943

SPECIAL CONTRIBUTIONS

PENICILLIN : ITS PROPERTIES AND POWERS AS A THERAPEUTIC AGENT by Professor L. P. Garrod	2
THE DISCOVERY OF PENICILLIN by Professor A. Fleming	4
THE DISCOVERY OF THE CHEMOTHERAPEUTIC PROPERTIES OF PENICILLIN by Dr. E. Chain & Professor H. W. Florey	5
PENICILLIN FOR SELECTIVE CULTURE AND FOR DEMONSTRATING BACTERIAL INHIBITIONS by Professor A. Fleming	7
OTHER ANTIBACTERIAL SUBSTANCES FROM BACTERIA AND MOULDS by Dr. E. Chain	8
CLINICAL USES OF PENICILLIN by Dr. M. E. Florey	9

REVIEW OF SELECTED PAPERS

Discovery : Early Investigations : Bacteriological Applications

1929 First Description ; Production : Selective Bacteriostasis	13
1930 Use for Isolation of <i>H. Influenzae</i> (Pfeiffer)	14
1932 { Uses in Bacteriology (and as a Wound Dressing)	14
{ Observations on Production and Extraction	15
1937 Use for Isolation of <i>H. pertussis</i>	15
1942 Use for Isolation of <i>Acne Bacillus</i>	15

Chemotherapeutic Action : Pharmacology : Bacteriological Investigations

1940 { First Cure of Experimentally Infected Animals : Preliminary Report on Pharmacology	15
{ Inactivation by a Bacterial Enzyme—Penicillinase	16
{ Morphological Effects on Bacteria	16

First Clinical Trials : Production : Biological Properties

1941 Successful Trials in Human Infections : Laboratory Large-Scale Production : Assay : Extraction : Antibacterial Action : Toxicity : Pharmacology	16
--	----

Further Chemotherapeutic, Bacteriological, and other Investigations

1942 { Biological Properties of Purer Samples : Calcium Salt	18
{ Methods of Testing Bacteriostasis	18
1942-3 Further Experimental Clostridial Infections	19
{ Experimental Staphylococcal Lesions of the Eye	19
{ Experimental Pneumococcal Lesions of the Eye	19
{ Negative Experiments with Viruses	20
{ Synergistic Effect of Para-aminobenzoic Acid and Sulphapyridine	20
1943 { Inhibitory Action on Urease	20
{ Production : Methods of Increasing the Yield	20
{ Rapid Method for Assay	20
{ Elimination from Culture Media by Penicillinase	21
{ Effect on Tissues	21

Purification and Investigation of Chemical Properties

1942 { Purification and Some Physical and Chemical Properties	21
{ Spectrographic Examination of Preparations	21
{ Purification and Chemistry	22
1943 { Penicillamine, a Degradation Product	22
{ Penillic Acid	22

Further Clinical Trials

1941 Local Administration in Nasal Carriers of Staphylococci	22
{ Methods and Rationale of Local and Systemic Administration in a Series of Cases	23
{ Elimination of Streptococci and Staphylococci from Burns	24
1943 { Local Treatment of War Wounds	24
{ Detailed Report on Intrathecal Administration in a Case of Streptococcal Meningitis	24
{ Treatment of War Wounds in North Africa	25
{ Infected Burns and Surface Wounds	26

APPENDIX

The Oxford Unit	26
The Slide-Cell Technique	26
Communications Published in Britain but not Reviewed in this Number	26
Communications Published in Other Countries	26

Interest in penicillin is becoming world-wide, but war-time disturbances of communications have added to the difficulty in some countries of obtaining access to the relevant literature, which covers a span of 15 years and is distributed among journals of divergent character.

These circumstances seemed to indicate that a useful purpose might be served by a special number of this Bulletin devoted entirely to a survey of penicillin, from the date of its discovery to the close of 1943—the year in which clinical trials on a more adequate scale became possible.

Acknowledgment is due to the authors who have found the time—in some cases at very short notice—to contribute articles to this number.

Professor L. P. Garrod has already been the subject of a note (BMB 48) in this Bulletin. He is a member of the Penicillin Therapeutic Trials Committee of the Medical Research Council, and has for many years been studying the chemical control of bacterial infections. His writings on this subject reveal a rare gift of lucid exposition.

Professor Alexander Fleming, the discoverer of penicillin, has been occupied in the study of chemical antibacterial agents and their effect on the normal defences of the body since the war of 1914–18. He has also been deeply interested in certain physiological antibacterial agents, such as lysozyme, and in bacterial antagonisms. He is Professor of Bacteriology in the University of London and Assistant Director of the Inoculation Department of St. Mary's Hospital. In 1943 he was elected a Fellow of the Royal Society.

Professor H. W. Florey graduated at Adelaide University,

Australia, in 1921 and came to England as a Rhodes Scholar in 1922. He has done original work in various fields, notably on the mechanism of inflammatory changes, and has travelled widely. In 1935 he was elected Professor of Pathology at Oxford. In more recent years his attention has been increasingly directed to the study of bacterial inhibition, and it was this interest in the general problem which led him, with his Oxford team of scientists, to discover that penicillin can be purified and used as a chemotherapeutic agent. Professor Florey became a Fellow of the Royal Society in 1941.

Dr. E. Chain is University Demonstrator in Chemical Pathology in the Sir William Dunn School of Pathology, Oxford. He has published many papers on various biochemical problems. His chief interests have been the study of enzymes and the isolation of physiologically active substances from natural sources. He has been closely concerned throughout with chemical and biochemical work on penicillin.

Dr. M. E. Florey is, like her husband, a medical graduate of Adelaide University. She played a leading part in the early clinical trials at Oxford, and has since made a detailed study of the effects of penicillin applied locally. She is at present engaged in exploring fresh fields of clinical application.

Acknowledgment is due to Dr. E. P. Abraham, Dr. M. A. Jennings and Dr. A. G. Sanders, all of the School of Pathology at Oxford, for the preparation of abstracts for the "Review of Selected Papers." Dr. Jennings, in addition to contributing many abstracts and providing references for the bibliographies, has given much valuable help at all stages of the preparation of this number.

SPECIAL CONTRIBUTIONS

197

PENICILLIN: ITS PROPERTIES AND POWERS AS A THERAPEUTIC AGENT

LAWRENCE P. GARROD, M.D., F.R.C.P.

from the Department of Pathology, St. Bartholomew's Hospital, London

Chemotherapy of bacterial infections, which had been no more than an ideal until 1935, became a reality with the advent of prontosil. During the rapid development of sulphonamide treatment which followed, other organisms than *Staphylococcus pyogenes* were found to be susceptible, and successful attacks on *Gonococcus*, *Meningococcus* and *Pneumococcus* followed in swift succession. It seemed likely at the time that with the advent of new drugs of this type all bacterial infections could be brought under control. This hope has been disappointed, and for some years we have been discovering the limitations of sulphonamide treatment rather than extending its scope. Even among the most susceptible bacteria some strains occur with exceptional resistance to the sulphonamide drugs, while there are many species relatively or wholly resistant to them.

Another great therapeutic discovery has now been made, which provides a remedy for some of the infections in which sulphonamides fail. That it will do in certain cases what these drugs will not is only part of its claim to our interest: it is a substance with hitherto unheard-of—almost unimagined—properties. It combines enormous antiseptic power with such a degree of freedom from toxicity to the mammalian body that one thousand times the concentration necessary for therapeutic action can be produced in the blood without ill effect. Such a combination of deadliness to bacteria with harmlessness to the body is more than the most sanguine chemotherapist can have pictured as possible before the properties of penicillin became known. Treatment with it is governed not by the fear of over-dosage, but only by anxiety to employ so precious a remedy with the utmost possible economy.

The two principal stages in the evolution of penicillin as a therapeutic agent are described in succeeding articles by the discoverers themselves, Professor Alexander Fleming, of St. Mary's Hospital, London, and Dr. E. Chain and Professor H. W. Florey, of the University of Oxford. In other articles in this number Professor Fleming describes the use of penicillin in bacteriological techniques, Dr. Chain refers to other antibiotics, and Dr. M. E. Florey reviews the clinical uses of penicillin.

It is my task to present a general picture of what penicillin now is and what it will do, as an introduction to the more detailed clinical contributions which follow. Penicillin is now being produced on a considerable and rapidly increasing scale, in both England and the U.S.A., by extraction from mass cultures of *Penicillium notatum*. No other method of production is yet known, although synthesis is an eventual possibility. In each of these countries the output has been officially controlled, and supplies have been afforded for clinical trials only to chosen investigators. In England not only the original employment of penicillin as a therapeutic agent but much of the subsequent study on which our present knowledge is based has been due to the enterprise of Florey himself and his colleagues.

The Properties of Penicillin

Penicillin is an unstable acid, and the preparations used in therapeutics are its salts. The sodium salt employed for systemic treatment is hygroscopic and somewhat less stable than the more easily handled calcium salt, which is used mainly for local application. Potency is expressed in Florey¹ [Oxford] units, an arbitrary amount determined by comparison with a standard preparation. Pure penicillin would have a potency of at least 1,000 units per mg.; that in present use is far from pure—owing to the serious loss of active substance which further purification entails—and material with a potency of 100 units or less per mg. is quite satisfactory for clinical use. It has been shown experimentally that an increase in purity diminishes toxicity, and clinical experience has shown that untoward effects such as pain on intramuscular injection and fever or thrombophlebitis following intravenous administration are caused mainly by products of low potency. These effects are thus due to impurities rather than to penicillin itself.

In the presence of penicillin, even in very low concentration, certain species of bacteria not only cannot multiply but slowly die. Whether this effect is "bactericidal" or purely "bacteriostatic" is not clear; the distinction is not easily

¹ [see BMB 239]

made, and the mechanism of the effect is unknown, although the peculiar changes in bacterial morphology first observed by Gardner¹ suggest that at least the process of division is inhibited. More important from the practical standpoint is the fact that this effect is exerted as well in serum, blood, or even pus, as in a simple medium such as broth. Within wide limits it is also independent of the number of bacteria present. Yet even very high concentrations are without effect on the activity of leucocytes: both by this form of study and by several others penicillin has been shown to have almost no local tissue toxicity. These facts explain the superiority of penicillin over sulphonamides for direct application to wounds; concentrated sulphonamides are by no means altogether non-toxic, they are far from indifferent to bacterial numbers, acting best when only few are present, and they are inhibited by the breakdown products in pus. Penicillin overcomes all these difficulties, and the consequent difference in effect is fully equal to expectation.

It is essential to understand that penicillin exerts this action only on certain species of bacteria; it is indeed the most highly selective antiseptic known, and for years was used by Fleming as an agent in selective culture media, which prevented the growth of some bacteria and permitted that of others. Most of the susceptible species are gram-positive; they include the three main pyogenic cocci (*Staphylococcus*, *Pneumococcus* and *Streptococcus pyogenes*), the gas gangrene group (among which *Cl. adematians*, although resistant to sulphonamides, is almost as susceptible as *Cl. welchii* to penicillin), *B. anthracis* and *C. diphtheriae*. The only fully susceptible gram-negative species are *Neisseriae*, the gonococcus and meningococcus. Among resistant organisms are the tubercle bacillus and almost all gram-negative bacilli, including the typhoid-dysentery group (some of which are slightly sensitive), the genera *Brucella* and *Hæmophilus*, and two frequent wound invaders, *Proteus* and *Ps. pyocyanea*.

Systemic Penicillin Treatment

Penicillin can be used therapeutically in two ways: It can be applied locally, or administered by parenteral injection so that it circulates in the blood and reaches every part of the body. The former method is economical but often difficult and sometimes inapplicable, the latter sure in its effect but immensely costly, using as a rule at least fifty times the amount needed for local treatment. Penicillin is absorbed from the alimentary tract, but cannot be given by this route because much of it is destroyed by acid in the stomach or by bacteria during rectal infusion. It must therefore be injected, either intramuscularly or intravenously. Unfortunately it is rapidly excreted in the urine, and the maintenance of an adequate blood level has been aptly compared by Florey to an effort to keep a bath full with the plug out. Such a level can, however, be maintained by continuous intravenous infusion or by intramuscular injections at intervals of not more than three hours day and night, the daily dose for an adult being about 120,000 units. This may have to be continued for seven days or even longer. A sudden and dramatic improvement is rarely seen, and sustained treatment, arduous for those in charge and disagreeable for the patient, is the price of success.

In present circumstances it is unjustifiable to administer penicillin systemically for any condition amenable to sulphonamide treatment. Septicæmia due to *Strept. pyogenes* or *Pneumococcus* is therefore treated only in the exceptional cases found to be sulphonamide-resistant. Staphylococcal septicæmia is always relatively resistant to sulphonamides, and penicillin, when available, is more decidedly indicated for this condition than for any other. Apart from septicæmia, extensive and deep-seated infections inaccessible by local applications require systemic treatment; these include osteomyelitis, severe cellulitis and gas gangrene. It has recently been shown by Florey and Cairns in battle casualties from Sicily that potentially infected compound fractures can be closed with the aid of this treatment. American experience suggests that sulphonamide-resistant pneumococcal pneumonia will respond to a very short course, and observations made in both the American and British armies have shown that cases of gonorrhœa can be cured by a total dose of little more than 100,000 units given in a space of about 24 hours. With more experience and larger supplies, further and more precise indications for this form of administration will doubtless be obtained.

Local Penicillin Treatment

The local application of penicillin takes many forms, some calling for ingenuity which is well rewarded by the remarkable effects to be obtained at little cost. Application to burns and other superficial and accessible wounds is secured by a cream or powder, the only satisfactory diluent known for the latter being sulphanilamide. These preparations can be relied on to eliminate infection by hæmolytic streptococci and staphylococci from such areas. Similar applications are highly successful in the treatment of skin infections such as impetigo and sycosis barbæ. The treatment of deeper wounds demands arrangements whereby a preparation can be enabled to penetrate them completely and persist there. A radical change in surgical technique is often necessary to secure this. Thus an abscess cavity or other infected area which would normally be laid widely open and drained freely may either not be incised at all but treated by aspirations and injection of penicillin solution, or if incised, it may be sutured again and closed, except for a small aperture containing a tube through which the solution is introduced at intervals afterwards.

The various applications of this principle are too numerous to detail here. Historically the first was the modified operation which enabled the Floreys to treat mastoiditis, and the latest, and at present the most important, is the closure of recent soft-tissue battle wounds advocated by Florey and Cairns on the strength of their recent experience in North Africa. Much more remains to be done in devising methods of using penicillin to good effect locally in the infinite variety of wounds, sinuses and other lesions to which it can be applied.

Common causes of failure are morbid anatomical conditions such that the solution either does not reach all parts of the lesion or does not persist there, the presence of bacteria which are resistant to penicillin or actually destroy it, and antecedent fibrosis mechanically preventing closure and healing.

A special example of local treatment is the intrathecal injection of penicillin solution for the treatment of meningitis. This has been highly successful in a few cases, and is imperative for treating this condition, since penicillin, unlike the sulphonamides, does not pass freely from the blood into the cerebrospinal fluid.

Future Prospects

The time may not be very far distant when penicillin will become generally available, at least in limited quantities. This will certainly happen soon after the war is over, when military surgery, which now has priority over other demands, no longer calls for a large supply. It is therefore perhaps not too early to issue a warning that the successful use of penicillin is by no means as easy as treatment with sulphonamides. It has so far been exclusively in the hands of experts under research conditions, who have obtained good results only by unremitting care and with the aid of strict laboratory control. The duties of the laboratory in connection with penicillin treatment are very onerous. It is necessary first to determine the nature of the infection and the sensitivity to penicillin of the organisms concerned. Local treatment should then be controlled by frequent further cultures. Systemic treatment calls for repeated estimations of the penicillin content of the blood in order to verify adequate dosage. Owing to its instability and liability to contamination with resistant bacteria, penicillin should also be dispensed by the bacteriologist rather than the pharmacist. Without such services in addition to expert surgical and nursing care, any but the simplest forms of penicillin treatment may easily fail.

Looking further into the future, it may be asked what prospects there are of extending the scope of this treatment. The full possibilities of penicillin itself have not yet been explored, even in infection by bacteria known to be susceptible. For example, little is yet known about its effect in gas gangrene, and still less about syphilis, diphtheria or anthrax. But is there any possibility that substances related to penicillin will be found which attack bacteria on which penicillin has little or no action? A systematic study of other moulds has been in progress for several years, and so far none has been found which produces an antibacterial substance equal in therapeutic value to penicillin, although hundreds of species have been tested. Some of these sub-

¹ [see BMB 211]

stances do, however, act on a wider range of bacteria including gram-negative bacilli. This property has not yet been found uncombined with toxicity to mammalian tissues. The other possible approach is the synthetic. When the structure of penicillin becomes known it may be possible so to vary it

that a wider range of activity is secured. One thing quite certain is that penicillin differs fundamentally from other antibacterial agents. Its discovery is an achievement of the first magnitude, of which the ultimate consequences cannot yet be foreseen.

THE DISCOVERY OF PENICILLIN

ALEXANDER FLEMING, M.B., F.R.C.S., F.R.S.

from the Inoculation Department, St. Mary's Hospital, London

I have been asked to say how I came to discover penicillin. After a lapse of fifteen years it is very difficult to say just what processes of thought were involved, but it seems necessary to go back much further than 1928 when the activity of penicillin was first observed.

Antecedent Investigations

As one of the pupils of Sir Almroth Wright I had naturally been deeply interested during the whole of my career in the destruction of bacteria by leucocytes. During the 1914-18 war I spent much time investigating problems in connexion with septic wounds, and I was then impressed with the antibacterial power of the leucocytes contained in pus which exuded from septic wounds. It was also clear from these investigations that the chemical antiseptics in common use were more destructive on the leucocytes than they were on bacteria.

This interest in antiseptics and leucocytes was continued in post-war years, and in 1924 I was able, by a simple method, to demonstrate clearly the antileucocytic power of antiseptics, and to indicate that if the antileucocytic action of an antiseptic were greater than its antibacterial action, such antiseptic was unlikely to be successful in the treatment of a septic wound.

In 1922 I described lysozyme, a powerful antibacterial ferment occurring naturally in human tissues and secretions, in the white of the domestic hen's egg, and elsewhere.

Effect of Contamination of a Culture

In September 1928 I was working on the variation of staphylococcus colonies following on a publication by Professor Bigger, who had shown that colonies of widely different appearance could be produced from a pure culture of an ordinary pyogenic staphylococcus. In the course of these observations culture plates of staphylococci were examined at intervals with a dissecting microscope, which involved a temporary removal of the cover and exposure to contamination from the air. After examination, some of the culture plates were placed in the incubator and others were left to mature at room temperature. Further examination of one of the latter showed that a mould colony had developed towards one side of the culture plate. Such contamination with a mould was, in the circumstances, not unexpected, but what was astonishing was that in this particular culture plate the staphylococcal colonies for some considerable distance round the mould growth were obviously undergoing lysis. What had originally been a well-grown staphylococcal colony was now a faint shadow of its former self.

It is certain that every bacteriologist has not once but many times had culture plates contaminated with moulds. It is also probable that some bacteriologists have noticed similar changes to those noted above, but that, in the absence of any special interest in naturally occurring antibacterial substances, the cultures have simply been discarded.

It was, however, fortunate that, with the background I have briefly sketched, I was always on the lookout for new bacterial inhibitors, and when I noticed on a culture plate that the staphylococcal colonies in the neighbourhood of a mould had faded away I was sufficiently interested in the antibacterial substance produced by the mould to pursue the subject.

Experimental Observations

The next step was to touch the mould colony with a platinum wire and transfer some spores to a culture tube of

Sabouraud's medium which, to the ordinary bacteriologist, is the usual medium for growing moulds. It is interesting that until recently all the penicillin used clinically had been produced from sub-cultures of this original tube. This first pure culture of the mould has not survived the years, but the original culture plate with the mould colony inducing dissolution of staphylococcal colonies still exists [see Fig. I]. The

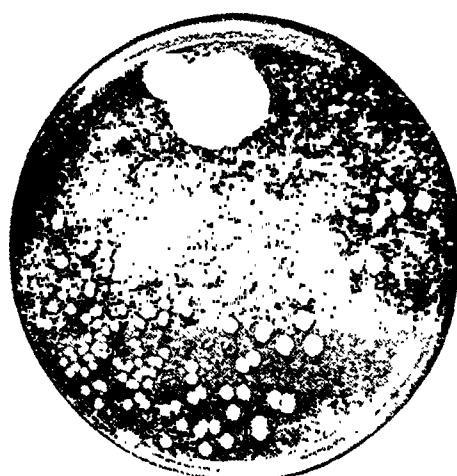


FIG. I.—This photograph shows the original contaminated culture which led to the discovery of penicillin. The patch at the top is the growth of mould (*Penicillium notatum*). In the lower third, normal staphylococcal colonies are seen. For some distance around the mould, the growth of staphylococci has been suppressed.

Until recently, all penicillin produced in Britain and the U.S.A. was derived from sub-cultures of the mould colony shown in this photograph (which is reproduced from Fleming's 1929 paper in the *British Journal of Experimental Pathology*).

preservation of this culture shows that, although I was unable to concentrate the antiseptic substance sufficiently for therapeutic use, I yet considered the culture a memorable one.

Having got a pure culture, I grew it in the ordinary nutrient broth used by bacteriologists. It grew as a felted mass on the surface. After a week it was found that the culture fluid diluted some 500 to 800 times would completely inhibit the growth of staphylococci, and it was therefore some two or three times as strong in that respect as pure carbolic acid. It was obvious from this that the antibacterial substance produced by the mould was a remarkable one and demanded further investigation.

The mould belonged to the genus *Penicillium*, so that the active substance, which was then (and still is at the time of writing) of unknown chemical constitution, was christened "penicillin." The mould was later identified as *Penicillium notatum*, a species which had been found by Westling in decaying hyssop in Norway (Thom).

From the appearance of the original plate it was obvious that penicillin was readily diffusible in agar, just as was lysozyme, which I had investigated some six years earlier. The technique which we had used with lysozyme was applicable to penicillin. One method used and figured in my original paper was to cut out a strip of agar from a culture plate, plant various bacteria in streaks at right angles to the gutter thus formed, and then fill the gutter with agar mixed with penicillin. The active substance diffused into the agar and inhibited the different bacteria for a distance varying with their sensitivity to penicillin. Some, such as *B. coli* or

H. influenzae, were not inhibited at all, while others, such as *Staphylococcus*, *Streptococcus*, *Pneumococcus*, *Gonococcus*, and the diphtheria bacillus would not grow anywhere near the penicillin strip [see Fig. II]. It was therefore clear that

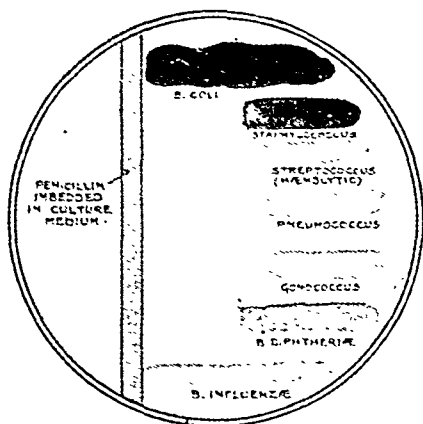


FIG. II—This drawing, also reproduced from Fleming's 1929 paper, shows the differential bacteriostatic effect of a penicillin-containing fluid in a gutter made by cutting out a strip from the agar medium. Inocula of various bacteria have been made at right angles to the gutter. Growth of *B. coli* and *H. influenzae* is not inhibited at all, while growth of the other organisms is inhibited in varying degrees.

penicillin had a specific action on some bacteria and did not affect others, and it is interesting that the bacteria originally found to be sensitive in this way to the crude culture fluid are the same as those which have subsequently been found to be affected by concentrated penicillin used clinically.

In view of the results I had previously obtained with the chemical antiseptics in common use, I proceeded to test

¹ [see BMB 203]

² [see BMB 241]

³ [described in BMB 200]

⁴ [described in BMB 199]

whether, like these, penicillin was poisonous to human leucocytes. It had no poisonous effect, nor was it toxic when injected into animals.

Conclusions

Here, then, we had an antiseptic substance which at that time was unique in having a strong inhibitory effect on many of the common bacteria which infect the human body, but which was not toxic to animals or to human leucocytes. Unfortunately it was a very unstable substance, and early attempts to concentrate it had little success. Although some tentative observations on the local antiseptic action of the crude fluid were made with moderate success, its instability and the smaller number of septic cases in hospital in peace time led to its clinical use not being seriously pursued.

The laboratory results, however, together with the few clinical observations, made me state in the summary of my original paper ¹ in 1929 that:

"It may be an efficient antiseptic for application to, or injection into, areas infected with penicillin-sensitive microbes";

and in 1931 in an article ² on the use of antiseptics:

"It is quite likely that it, or a chemical of a similar nature, will be used in the treatment of septic wounds."

The words "chemical of a similar nature" were prompted by the thought that some day a chemist would discover the nature of the active principle, synthesize it, and use either that or some modification as a chemotherapeutic agent. That was years before the introduction of the sulphonamides, and at a time when the only effective antibacterial chemotherapy was the treatment of syphilis by modifications of Ehrlich's salvarsan.

I have used penicillin constantly since 1929 for differential culture,³ but its use for practical therapeutic purposes remained in abeyance until the Oxford workers started their investigations.⁴

THE DISCOVERY OF THE CHEMOTHERAPEUTIC PROPERTIES OF PENICILLIN

E. CHAIN, Ph.D., & H. W. FLOREY, M.B., Ph.D., F.R.S.

from the Sir William Dunn School of Pathology, Oxford

Professor Fleming has described how he discovered that the mould *Penicillium notatum* produces a substance which inhibits the growth of certain pathogenic bacteria, and the experiments which he performed with this substance. In this article we propose to trace the steps which led to the discovery of the chemotherapeutic properties of penicillin and eventually to its employment in treating diseases in man.

Planned Investigation of Antibiotics

It may be of interest to know why the work was taken up in Oxford. In 1929 one of us (H. W. F.) started work on an antibacterial substance, lysozyme, which had been discovered by Fleming in 1922. During the 1930's this work was carried on till the enzyme was purified by Roberts (1937) and its substrate was characterised (Epstein & Chain, 1940). During the later part of this work the present writers prepared a plan for the systematic investigation of antibacterial substances produced by micro-organisms. It was thought that these might be chemically and biologically interesting, especially as many of them were active against pathogenic bacteria.

As long ago as 1877, Pasteur & Joubert noticed that the growth of certain air-borne organisms inhibited the growth of the anthrax bacillus, and suggested that this fact might be of importance in therapeutics. Since that time, many instances have been found of the production of a substance by one microbe which inhibits the growth of others. These inhibitions are due to metabolic products, recently termed "antibiotics."

Attempts had been made to utilise these substances in medicine, the most noteworthy being that of Emmerich &

Loew (1899) who extracted "pyocyanase" from *Ps. pyocyanea*, and Dubos (1939) who extracted gramicidin, a mixture of two polypeptides, from *B. brevis*.

The Oxford work on antibiotics began to develop in 1938. Of a number of known antibiotics considered, "pyocyanase" and penicillin were chosen for the first investigations. It appeared from reports in the literature that the latter substance was unstable and therefore difficult to extract, but the fact that it was active against a range of important pathogenic organisms weighed the balance in its favour. Moreover, both Fleming (1932) and Clutterbuck, Lovell & Raistrick (1932), had stated that penicillin activity might, under certain conditions, be retained in the culture medium for some weeks. It seemed worth while to see whether appropriate conditions could be found for extracting the substance, so that further examination of both its biochemical and biological properties could be made.

Physical and Chemical Properties of Penicillin

It was first established that penicillin was an acid which, as the free acid in aqueous solution, was very unstable, but in the form of alkali and alkaline earth salts was stable between pH 5 and pH 7. Clutterbuck *et al.* had found that penicillin was extracted into ether on shaking with the culture fluid after it had been acidified. When the ether was evaporated, however, the activity was largely lost. This experiment was confirmed, but it was found possible to prepare stable salts of penicillin by shaking the ether solution with dilute aqueous alkali so as to bring the final pH to 7. In addition to ether, a number of organic solvents, for example chloroform and amyl acetate, could be used to extract the free acid form of

penicillin. The salts of penicillin were much more soluble in water than in the organic solvents, and therefore penicillin was removed from the organic solvent by about $\frac{1}{5}$ to $\frac{1}{10}$ the volume of alkali solution. A concentration of penicillin was thereby achieved, and by repeating the extraction several times with different solvents and at suitable pH, a considerable purification of penicillin and simultaneous reduction of the bulk of liquid was obtained.

The losses of penicillin during these operations were small if the solutions were kept cold throughout. On drying the final aqueous solution *in vacuo* from the frozen state, a preparation of a salt of penicillin was obtained, in powder form, which kept its antibacterial activity unchanged for a long time.

Methods of Purification

Chemically, however, the preparation was far from pure, containing, as is now known, not more than a small percentage of pure penicillin. The isolation of penicillin in the pure state from this mixture proved a difficult problem because of its instability towards many reagents and the unfavourable solubilities of the free acid and its salts. It was found that penicillin was destroyed by dilute acid and alkali, by many heavy metals (in particular zinc, cadmium, copper and mercury), and by primary alcohols, ketonic reagents and oxidising agents. The stable alkali and alkaline earth salts of penicillin were extremely easily soluble in water, and no organic cation forming a relatively insoluble salt with penicillin suitable for purification purposes was found.

The selection for the methods of purification of penicillin was therefore limited to distribution between different solvents and water, and to adsorption methods. Chromatographic methods have been used extensively. In combination with a reduction process with aluminium-amalgam it has been possible by these methods to produce penicillin preparations from which crystalline salts could be made. The purest material obtained at Oxford has an activity of about 1,000 Oxford units per mg., and is capable of inhibiting the growth of certain bacteria at a dilution of about 1 : 50,000,000.

Bacteriostatic Properties, Pharmacology, Chemotherapeutic Action in Animals

Once a protein-free preparation containing a stable salt of penicillin was obtained it became possible to examine in detail its biological properties.

For the first biological experiments very crude preparations are used. Their antibacterial properties proved to be the same as those found by Fleming, who used crude penicillin-containing culture fluid. It was noted in addition that *Actinomyces bovis* and the group of anaerobic organisms using gas gangrene were sensitive, but unfortunately not the tubercle bacillus.

So great was the antibacterial power of even the crudest extracts that at that time—not realising the extraordinary potency of penicillin—we believed them to be fairly pure. In actual fact we know now that they contained about 1 % of pure penicillin. However, on the assumption that they were fairly pure, certain biological investigations were undertaken.

It was shown that the extracts were remarkably non-toxic to mice—a 20 g. mouse showed little or no disturbance after injection of 10 mg. of the sodium salt. It has since been found that 20 mg. of a much more highly purified extract can be given without any deleterious effects. Not only were the extracts relatively innocuous to the whole animal, but leucocytes and tissue cultures withstood many hundreds of times the concentration needed to inhibit such organisms as the streptococcus. In the light of present knowledge of the gross impurity of the original extracts, one can only be thankful that the mass of impurities, as well as the penicillin, were so little toxic.

Penicillin was readily absorbed in animals after intramuscular or subcutaneous injection, and from the small intestine. It could not of course be given by mouth because the acid of the gastric juice destroyed it, nor by rectum as the bacteria present there inactivated it. It was largely excreted, still in an active form, in the urine of the mouse, rabbit and cat, and to a certain extent in the bile and saliva, though not in the tears or pancreatic juice of the cat. Though penicillin was readily soluble and diffusible, it did not pass in detectable quantities from the blood into the cerebro-spinal fluid.

In agreement with Fleming's observations it was found that the action of penicillin was bacteriostatic, in that it

merely inhibited the growth of organisms and did not kill them quickly, as did poisonous antiseptics such as proflavine. The respiration of bacteria, as measured in a Warburg-Barcroft apparatus, was not affected by quite strong solutions, in contrast to most antiseptics which, acting on some protoplasmic constituent, rapidly cause the cessation of respiration. This bacteriostatic effect was reflected in the morphological changes undergone by sensitive bacteria when grown in a dilution of penicillin not sufficient to cause complete inhibition of growth. By interference with division, giant forms were produced.

Most antibacterial substances such as ordinary antiseptics and the sulphonamides are, for one reason or another, not active in the presence of pus, and hence their therapeutic efficacy is severely limited. It was therefore a particularly fortunate property of penicillin that pus, tissue autolysates, blood and serum had no inhibitory effect on its activity. It was found too that the number of organisms present had little effect on its inhibitory power—again a contrast with the sulphonamides.

In view of this combination of great antibacterial power with low toxicity, it was not altogether surprising that "mouse protection tests" gave a clear demonstration of the chemotherapeutic properties of penicillin. With appropriate dosage almost complete protection was afforded to batches of mice infected intraperitoneally with lethal doses of streptococci and staphylococci and intramuscularly with *Cl. septicus*.

Early Observations on Human Subjects

It will be seen from this account that a fairly complete knowledge of its properties, both chemical and biological, had been obtained before penicillin was used on man. In terms of the labour involved it was, however, a big step from experiments on mice to making observations on the human subject, for the mould produces very little of the active substance. Months elapsed before enough material could be accumulated to try the first injection on man.

Injection in the human subject disclosed that some substance was present in the crude penicillin preparations which caused a rigor and sharp rise of temperature. This had not been suspected from observations in animals. By good fortune the pyrogenic effect was due not to the penicillin but to an impurity which could be removed.

Insufficient material had been accumulated for the first 2 cases treated, and although both patients, who were seriously ill, did well for a time, they relapsed and further treatment could not be carried out for lack of material.

In the course of some months enough was accumulated (partly prepared in Oxford and partly in the laboratories of *Imperial Chemical Industries*) to treat by parenteral injection a further 18 patients. During the course of these observations it became clear that the behaviour of penicillin in man was no different from its behaviour in mice and cats. Toxic reactions, apart from the pyrogen, were not observed and some striking recoveries of patients infected with staphylococci were obtained. Suitable dosage was worked out and the principles of treatment were formulated. At the same time, penicillin was shown to be valuable for local application in various septic conditions.

Industrial Production and Chemistry

Considerable interest was aroused both in Britain and in the U.S.A. by the demonstration of the chemotherapeutic possibilities of penicillin in naturally occurring disease in man. All the main facts have now been amply confirmed and commercial firms and others are continually improving and developing methods of very large scale production by mould fermentation. One of the chief obstacles to be overcome in large-scale work is the destruction of penicillin which is brought about by the enzymes of many air bacteria. The most careful precautions against contamination are necessary at all stages of growth of the mould.

Immediately after the chemotherapeutic properties of penicillin were established, work on the elucidation of its chemical constitution was actively pursued at Oxford, in the *Sir William Dunn School of Pathology* by Dr. E. P. Abraham and one of us (E. C.) in collaboration with Dr. Wilson Baker and Sir Robert Robinson in the *Dyson Perrins Laboratory*. Subsequently many other chemists both in England and America have started work on the penicillin problem. It is not possible at present to describe in detail the chemical work carried out, but it can be stated that it has led to the elucidation

tion of the chemical constitution of the breakdown products of penicillin and has opened the way to eventual synthesis.

While no doubt large quantities of penicillin will be produced by culture of the mould, there is little prospect that sufficient for general use will be available for some time to come. It is probable that, if synthesis can be achieved, a new range of chemotherapeutic agents will be produced with properties varying in different ways from those of the original substance.

Now that it appears probable that penicillin will be used on a very large scale it is interesting to look back on the early days when we were many times assured that it was too

unstable ever to be a practical proposition, and that in any case the vast amount of culture medium needed to produce small quantities of penicillin was an almost insuperable bar to its production.

We should like to emphasise that the work, covering as it did a wide field of investigation, could not have been carried through without the close collaboration of the various workers whose names appear on the papers concerned with penicillin which have come from this laboratory. The clinical work, too, was made possible only by the help and co-operation of many surgeons, physicians and bacteriologists.

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200

PENICILLIN FOR SELECTIVE CULTURE AND FOR DEMONSTRATING BACTERIAL INHIBITIONS

ALEXANDER FLEMING, M.B., F.R.C.S., F.R.S.

from the Inoculation Department, St. Mary's Hospital, London

My first (1929) paper on penicillin was entitled "On the Antibacterial Action of Cultures of a *Penicillium*, with Special Reference to their Use in the Isolation of *B. influenzae*." The sub-title was inserted because this, the isolation of *B. influenzae*, was the first practical application of penicillin.

In an article in 1932 I mentioned several uses of penicillin:

- For the isolation of insensitive bacteria from the midst of large numbers of sensitive organisms,
- for the demonstration of some bacterial inhibitions,
- for the treatment of infections by sensitive organisms.

The third use, undoubtedly its most important one, is dealt with elsewhere, but the first two can be briefly described.

Isolation of Insensitive Organisms

The human pathogenic organisms may be classified as follows:

<i>Penicillin-sensitive</i>	<i>Penicillin-insensitive</i>
Staphylococcus	Typhoid, Paratyphoid, Dysentery, Coli group
<i>Streptococcus pyogenes</i>	<i>V. cholerae</i>
Other hæmolytic streptococci (other than Group D)	Friedländer's bacillus
<i>Streptococcus viridans</i> (most)	<i>B. pyocyaneus</i>
Non-hæmolytic streptococci (most)	<i>B. proteus</i>
Pneumococcus	Hæmophilic bacilli
Gonococcus	Brucella
Meningococcus	<i>B. pestis</i>
<i>M. catarrhalis</i>	Enterococcus
Diphtheria bacillus	Non-pathogenic gram-negative cocci of the respiratory tract
Diphtheroid bacillus (most)	Tubercle bacillus
Anthrax bacillus	Yeasts
Actinomyces	Moulds
<i>B. welchii</i> and other clostridia	

A consideration of this table shows that it is in the respiratory tract that a differential medium containing penicillin is likely to be most valuable in clinical bacteriology. Here the staphylococci, streptococci, pneumococci, and diphtheroid bacilli are sensitive. These are the most commonly found bacteria, and if they are inhibited we are left with little else than Pfeiffer's bacillus, *B. pertussis*, Friedländer's bacillus, and a few non-pathogenic gram-negative cocci, and their isolation becomes easy.

I have already stated that the first practical application in 1929 of penicillin was the isolation of Pfeiffer's bacillus, and we have used it ever since for this purpose.

In 1930 Maclean and myself were able to show that hæmo-

philic bacteria were present normally in all human mouths and throats. In my original (1929) paper, also, I suggested its use for the isolation of *B. pertussis*, and it has since been used with great success for this purpose by Maclean (1937)

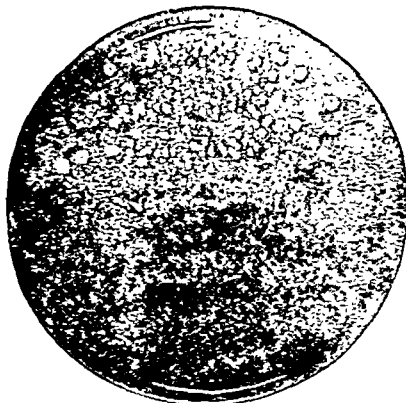


FIG. III—Another photograph reproduced from Fleming's 1929 paper. A culture plate was evenly inoculated with a mixture of staphylococci and *H. influenzae*. Six drops of the crude penicillin-containing solution were then spread over the lower half of the plate, with the result that staphylococcal growth was completely inhibited and a pure culture of *H. influenzae* was obtained. In the upper (untreated) half of the plate, there is a mixed growth of both organisms.

and others. This may prove to be its most important application in diagnostic bacteriology, as it is becoming more and more evident that the early bacteriological diagnosis of whooping cough is of the greatest importance in the control of the disease.

The behaviour of the gram-negative cocci towards penicillin is interesting. The pathogenic types, gonococcus, meningococcus, and *M. catarrhalis*, are among the most sensitive of bacteria, but the various non-pathogenic types normally found in the human mouth and throat are insensitive. Here, then, we have a simple test for the pathogenic types of these cocci which should have a useful application.

In other regions, too, a penicillin medium may be used for special purposes, and by its use in cultures from the puerperal vagina I was able to isolate hæmophilic bacilli in 2 out of 12 cases. A penicillin medium may be used in septic wounds to isolate various bacilli from among the staphylococci, and streptococci, which might obscure them, and I have sometimes found Pfeiffer's bacillus in septic

wounds by this method. On the other hand it is of little use in intestinal cultures, as here the most prominent organisms, and those which are most likely to obscure the others, are *B. coli* and its allies, which are all insensitive to penicillin.

I showed (1932), however, that potassium tellurite had a specific inhibitory action on bacteria which was almost the opposite of penicillin, so that a penicillin-sensitive organism was almost always tellurite-resistant and *vice versa*. Notable exceptions among human pathogenic organisms were the gonococcus, which was sensitive to both, and the enterococcus which was insensitive to both.

Thus by adding an inhibitory quantity of tellurite the penicillin-insensitive organisms were inhibited, and then by adding graded amounts of penicillin many interesting cultural results could be obtained.

Two methods were used for making differential cultures.

i. The infected material was spread on a plate containing a suitable culture medium and then 5 or 6 drops of penicillin (the solution used contained about 5 units per cm.³) were spread over half the plate. The untouched half of the plate therefore gave an ordinary mixed culture, while the penicillin-covered half grew only the penicillin-insensitive organisms. By reason of its simplicity, and of its giving complete and selective cultures on the same culture plate, this method is the most suitable for ordinary clinical purposes, and I have used it with great advantage ever since I introduced it in 1929.

ii. Penicillin may be incorporated in the culture medium in a strength of 0.5 to 1 unit per cm.³ In or on this medium the penicillin-sensitive microbes will not grow, and there remains a culture of only those organisms which are insensitive.

By carefully grading the strength of the penicillin, selective cultures can be made even among the penicillin-sensitive organisms. Thus Craddock (1942) showed that, by adding penicillin to glucose broth in a concentration twice that which would inhibit staphylococci, he was able to isolate the acne bacillus from pus which contained both the acne illus and staphylococcus.

he clostridia are not all equally sensitive to penicillin, it seems likely that, by a careful adjustment of the concentration, one type may be inhibited while another will grow ly, thus aiding in the separation of the different types.

Demonstration of Bacterial Inhibitions

When cultures are made from the post-nasal space in some irrrhal conditions, and one half of the culture plate is ted with penicillin, it is not unusual to find on one

side of that portion of the plate which is thickly planted a pure culture of pneumococcus or streptococcus, and a pure culture of Pfeiffer's bacillus on the other side. From such a plate it is quite clear that when a heavy inoculum is made the pneumococci or streptococci completely inhibit the Pfeiffer's bacilli, the presence of which is revealed when the cocci are prevented from growing by penicillin. It is true that, if the Pfeiffer's bacilli are present in sufficient numbers, they will grow and be recognised when the inoculum is so scanty that the individual colonies are sufficiently separated from the pneumo-streptococcal colonies to be outside the range of the inhibitory power, but when penicillin is used the result is dramatic and cannot be overlooked.

Even more striking results can be obtained by growing a colony of the mould (*P. notatum*) on a culture plate at room temperature for, say, three days. During that time it produces penicillin which diffuses into the culture medium for a distance of perhaps two centimetres. Then two highly coloured bacteria, one sensitive to penicillin (*Staphylococcus aureus*) and one insensitive (*B. violaceus*), are mixed in suitable proportions, and are streaked across the plate up to the mould colony. Near the mould colony only the violet coloured organism (*B. violaceus*) will grow, as the staphylococcus is inhibited by penicillin, but beyond the range of the penicillin the growth will be the bright orange colour of *Staphylococcus aureus*, which completely inhibits *B. violaceus*. Thus, by planting a mixture in such conditions, two pure cultures can be obtained in different parts of the streak. This result is even more dramatic if the cultures are made on a white paper disc placed on the surface of the culture medium. The nutrient material diffuses through the paper and allows growth on the surface, and the colours show up beautifully on the white background of the paper. This culture on paper has the additional advantage that it can be removed, sterilised with formalin vapour, and mounted on a card as a permanent specimen.

These are some of the laboratory uses of penicillin. With its more extensive employment, other useful applications will doubtless appear.

Even in the present days of penicillin shortage, the minute amount necessary for these laboratory uses can always be obtained. The crude culture fluid on which *Penicillium notatum* has grown is amply strong enough, and this can be produced with ease in any laboratory. Special culture media are unnecessary, as the ordinary nutrient broth of the bacteriologist will serve. Nor is an incubator a necessity, for the mould grows and produces penicillin at room temperature only a little more slowly than it does at its optimum temperature of 24° C.

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OTHER ANTIBACTERIAL SUBSTANCES FROM BACTERIA AND MOULDS

E. CHAIN, Ph.D.

from the Sir William Dunn School of Pathology, Oxford

The list below contains a selection of those antibacterial substances from bacteria and moulds which have been examined in some detail. A review of the early work on bacterial antagonism and antibiotics, up to 1941, has been published [29] and a review covering the more recent work is in the press [4].

Species	Antibiotic	Reference
Antibiotics Produced by Bacteria		
<i>Ps. pyocyanea</i>	pyocyanine	16, 17, 26
"	α-oxy-phenazine	26
"	lytic agent	26
<i>B. brevis</i>	gramicidin	15, 10
"	tyrocidine	10

Antibiotics Produced by Actinomycetes

<i>A. antibioticus</i>	actinomycin A.	31, 32
"	actinomycin B.	32
<i>A. lavendulae</i>	streptothricin	28, 33
<i>Proactinomyces</i> Gardner	proactinomycin	12

Antibiotics Produced by Penicillia

<i>P. notatum</i>	penicillin	
<i>P. claviforme</i>	claviformin (also	2, 5, 6, 9, 37
<i>P. patulum</i>	described as	
	patulin)	
<i>P. puberulum</i>	penicillic acid	1, 21
<i>P. cyclopium</i>		

Antibiotics Produced by *Penicillia*

<i>P. (Gliocladium) fimbriatum</i>	gliotoxin	11, 34, 35
<i>P. citrinum</i>	citrinin	25

Antibiotics Produced by *Aspergilli*

<i>A. flavus</i>	aspergillic acid	18, 19, 36
"	flavicin	3
<i>A. fumigatus</i>	fumigacin	30
"	fumigatin	20
<i>A. fumigatus mut. Helvola</i> Yuill	helvolic acid	7, 37
<i>A. clavatus</i>	clavacin	30
<i>A. giganteus</i>	gigantic acid	22

Two antibiotics produced by aspergilli, flavicin and gigantic acid, are very similar to penicillin in their chemical and biological properties. Thus it is evident that the production of penicillin-like substances is not confined to the species *Penicillium notatum* or even to the genus *Penicillium*.

All the other antibiotics, without exception, are less active against bacteria and more toxic to animal tissues than penicillin. With the exception of proactinomycin, helvolic acid and possibly streptothricin they are all protoplasmic poisons, exerting their antibacterial action by combining with a protoplasmic constituent common to all cells (proteins, lipids, etc.). However, the crude mixture of gramicidin and tyrocidine, designated as tyrothricin, has been used for the local treatment of infected wounds [15, 23, 24]. None of the other antibiotics has yet received such clinical trial.

Patulin, an antibiotic recently isolated from culture filtrates of *Penicillium patulum* [2] is identical with the previously described antibiotic claviformin [6, 9]. Like all ordinary antiseptics this substance is a general protoplasmic poison and is toxic to mice and leucocytes. Patulin has been stated by one group of workers to be effective in combating

the common cold [2], but another group of workers has not been able to confirm this claim [27].

The least toxic antibiotic, apart from penicillin, appears to be helvolic acid. This substance has many attractive properties from the chemotherapeutic point of view. It is very stable, and a bacteriostatic concentration can readily be maintained in the tissues. When it is given repeatedly, however, the liver suffers severe damage. When more facts about its chemical constitution become known it may be possible to reduce the toxic effect on the liver by modification of the molecule.

Though most of the antibiotics listed above have been obtained in the pure, crystalline state, the chemical constitution of many of them has not yet been elucidated. Several, e.g. gliotoxin (a sulphur-containing substance), proactinomycin (an alkaloid-like base), streptothricin and helvolic acid, as well as penicillin itself, are of chemical types hitherto unknown among antibacterial substances. The study of their structure provides many interesting problems and may lead to the synthesis of novel types of antiseptics and chemotherapeutic drugs.

Some antibiotics have in addition great biochemical interest. Thus gramicidin and tyrocidine belong to the very small group of crystalline polypeptides, and, as they are of relatively low molecular weight, the complete elucidation of their constitution may be possible [13, 14] with recently developed methods. This may throw some light on one of the most fundamental and difficult problems in biochemistry, the structure of proteins.

The antibacterial substance notatin [8] (also described as penicillin B or penatin), which is produced by *Penicillium notatum*, differs in nature from the antibiotics, being a glucose dehydrogenase which exerts its antibacterial action through the hydrogen peroxide which it forms. It has no action in the absence of glucose, nor in the presence of catalase, a constituent of all tissue cells. It is extremely toxic to animals and is unlikely to be of use in medicine.

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CLINICAL USES OF PENICILLIN

M. E. FLOREY, M.B., B.S.

from the Central Middlesex County Hospital

The successful application of experimental laboratory work to therapeutic measures could hardly be better exemplified than in the case of penicillin. Before any trial was made on man, almost the full range of infections capable of response to the drug was known. Equally important was the know-

ledge that the upper limit of dosage was not likely to be influenced by any toxic effect. Among the other inferences of practical importance that could be made from the laboratory work were: that oral administration of the unprotected drug would be ineffective because of its inactivation

by the acid gastric juice ; that frequent administration would be necessary because of the rapid concentration and excretion of penicillin by the kidneys ; that it would be unwise to prepare wounds for local application by cleaning with a number of the common antiseptics because of the inactivation of penicillin by heavy metals and by oxidation. The lack of any inhibitory effect on leucocytic activity by therapeutic concentrations of penicillin indicated that the disappearance of pus from lesions infected only by sensitive organisms would probably be a fair criterion of the elimination of sepsis.

With these facts already known, the main points still to be elucidated when clinical trials were begun were: adequate dosage, frequency and routes of administration and the most suitable methods for local application.

Clinical Trials

The earliest clinical trials, which included some 200 cases, were instigated by the *Sir William Dunn School of Pathology, Oxford* (Abraham, Chain, Fletcher, Florey, Gardner, Heatley & Jennings, 1941 ; Florey & Florey, 1943). They demonstrated the therapeutic effectiveness of the drug by both systemic and local administration. The cases chosen for treatment were pyogenic infections falling into the following categories :

Generalised infections accompanied by local lesions in bones, lungs and heart valves	Chronic blepharitis
Acute mastoiditis	Chronic sinus infections
Infections of the skin	Empyema
Infections of the conjunctiva, cornea and lacrymal sac	Synovitis
	A miscellaneous collection of infective conditions

The causal organism in the majority was the staphylococcus, in others it was the streptococcus or a combined infection by both organisms. A few infections were pneumococcal, gonococcal or due to actinomyces, and occasionally no organism sensitive to penicillin could be isolated.

The results of these early trials at Oxford may be summed up as :

Complete recovery	143 patients
Improvement	43 „
Little or no response	14 „
Total	200

These results appear striking enough to merit some consideration of the criteria adopted in ascribing recovery specifically to penicillin treatment. The first criterion was bacteriological. Pyogenic organisms present in lesions became scanty during treatment and eventually disappeared. Concurrently with their disappearance, the local and general signs of inflammation subsided, function returned, and healing began, these effects were considered as fairly attributable to removal of infection by penicillin. The fact that most patients treated in the first year or two of clinical trials were considered moribund, had not responded to any other treatment, or suffered from an infection which had persisted for many months or years without improvement, gave additional support to the conclusion that penicillin was the instrument whereby recovery took place.

About 150 cases of burns were also treated at about this time by Dr. Colebrook working for the *Medical Research Council* in the Burns Unit at Glasgow (Clark, Colebrook, Gibson, Thomson & Foster, 1943), and Flight Lieutenant Bodenham (Bodenham, 1943). No staphylococcal or streptococcal infection of a burn failed to disappear under adequate treatment. Healing was accelerated or successful skin grafts were carried out following the removal of the organisms from the surface of the burn.

Work in the U.S.A. has confirmed and amplified the British results mainly in systemic treatment (Keefer, Blake, Marshall, Lockwood & Wood, 1943). Of 500 cases reported, including some where the infection was not the only pathological condition (some cases were also suffering from cancer, aplastic anæmia, aneurism, etc.) the results were :

Recovery or improvement	366
No response	40
Deaths	94
Total	500

This series included 129 cases of gonorrhœa, of which the treatment was uniformly successful and subsequent reports (*Lancet*, 1943 ; Garrod, 1943) have confirmed the very rapid response to treatment in this condition irrespective of whether the infection is sulphonamide-resistant or not. Pneumonias were also treated with success, but the results recorded were by no means so striking as in gonococcal infections.

In neither the British nor the American series did recovery occur in subacute bacterial endocarditis (*Streptococcus viridans* infection) even after prolonged treatment.

In England, following the earliest trials, it was thought advisable to carry out a comparative trial of acute infections from which patients would in any event recover. By comparing penicillin-treated cases with similar acute infections treated by current methods the effects which might be attributable to the drug could be gauged.

Infections of the hands were chosen for this trial (Florey, M. E., & Williams, 1944). A hundred "control" patients were treated by recognised methods and a second 100 were treated in every way similarly except that penicillin was applied locally from operation onwards in place of (usually) hypochlorite preparations and (when considered necessary) sulphonamides by mouth. Bi-weekly bacteriological examinations showed that, in 75 % of control wounds, pyogenic organisms persisted from the first incision until complete healing. The remaining 25 % lost their infection or showed a diminished growth only when healing was far advanced. In 95 % of the penicillin-treated cases, these organisms had markedly diminished in numbers or had disappeared before the end of the first week.

From the clinical point of view this rapid elimination of sepsis resulted in the following marked differences :

Control	Penicillin-Treated
Continuance of pain and throbbing for variable periods following incision	Almost invariable relief of pain from incision and first application of penicillin onwards
Production of pus until healing was well advanced	Pus scanty or absent following operation
Formation of much granulation tissue with consequent contraction, limitation of movement, and sometimes painful scars	Little formation of granulation tissue. Rapid and more complete restoration of movement and smooth and painless scars
In severe infections, usually much sloughing, death of tendons and bone, and loss of digits	No loss of digits or any other tissue when treatment was begun at first operation

The retention of digits and restoration of function are particularly valuable assets in an industrial community where early return to work depends on full use of the hands. The working time saved to the 100 penicillin-treated cases totalled in the aggregate a number of years.

A further series of cases has been treated in the war zone (*Lancet*, 1943 ; Garrod, 1943). Here local application of the drug has enabled the early suturing of war wounds of the soft tissues to be carried out with almost uniform success. In no case did deleterious results follow this unorthodox treatment, although in some wounds complete union was not achieved and a few broke down. Results at 3 weeks were :

Complete union	104
Subtotal union	60
Failure	7
Total	171

In wounds complicated by compound fractures systemic as well as local treatment was employed, but the results were not so strikingly successful as in the soft tissue injuries. Results are improving, however, with developments in technique and the earlier administration of penicillin.

Gas gangrene was treated in 7 patients. The systemic route was used. Four of these patients recovered, but further improvements in results may well follow adaptations in the method of administration.

Of the penetrating brain wounds treated, some had an established infection, while others were treated within a few days, at a stage when infection had hardly developed. Results were satisfactory and healing occurred without fungus formation in all but one case. Three out of the 23 patients died, however, but in two of these the infection by gram-positive

organisms had been controlled and the third was inadequately treated.

This series of war injuries demonstrated well the successful and rapid results obtained when penicillin treatment is begun in the early stages of infection, rather than when the condition is so well established as to be less accessible either to local or systemic exhibition of the drug.

Investigations up to date have therefore shown the value of penicillin:

- i. As a preventive of infection in wounds, enabling a potentially septic wound to be treated in much the same way as an aseptic one,
- ii. in the promotion of healing in burns and for ensuring the success of skin grafts,
- iii. in infections (due to sensitive organisms) either (a) chronic, or (b) of such severity as to render the prospect of death likely, which have not responded to other forms of treatment,
- iv. in acute infections due to sensitive organisms,
- v. in the rapid curing of gonorrhoea including sulphonamide-resistant cases,
- vi. in pneumonia,
- vii. probably in gas gangrene, but here numbers have been few and methods not fully tried out.

Special Considerations

a. Excretion. Very early in the Oxford clinical trials the rapid excretion of penicillin by the kidneys was seen to be both a problem and an asset. In the days when every unit was precious, efforts were made to recover the drug from the patient's urine, but the labour and inconvenience were great and were justified only by the scarcity of material. The rapid deterioration of the penicillin when acted on by bacteria in the urine also made the yield very variable. One patient was able to pass urine every hour for 11 hours after a single dose. These specimens were assayed immediately and, although he was still excreting penicillin when the last specimen was taken, more than 75% of the dose was regained. Such was not the case when urine was collected in larger amounts and at longer intervals. Rammelkamp & Keefer (1943b), who have carried out detailed work on absorption, excretion and toxicity of penicillin, have also obtained variable yields from the urine, but it is not yet clearly established whether the total amount is excreted or whether part is destroyed in the body.

Its rapid elimination has been of value in determining the time taken for penicillin injected by various routes to reach the circulation and for a single dose to disappear. After intramuscular or intravenous injection, penicillin may be detected in the urine almost immediately, and after intrapleural injection within an hour. Penicillin is also concentrated by the kidneys, as after a single small dose it can be detected in the urine for well over 24 hours, even when the concentration has at no time been great enough to be detected in the blood by present methods. Administration for urinary infection has therefore been successful when repeated only once or twice in 24 hours, and staphylococcal and streptococcal urinary infections have been cleared up by doses which were relatively very small.

b. Effect on blood cells. On all cases treated from Oxford systemically and on many treated locally regular blood examinations were carried out. In no case was there a fall in the erythrocyte count during penicillin treatment, and in all severely ill cases, except one puerperal patient in whom a profuse lochia continued throughout treatment, there was an average rise of 250,000 to 500,000 erythrocytes per week. In view of the poor condition of the myocardium in septic patients, there seems therefore to be little indication for adding the strain of blood transfusion to the work of the heart. The leucocyte count appeared to give a good indication of the progress of the treatment. If it was low from toxæmia (or possibly from previous sulphonamide administration) at the beginning, it began to rise within 24 hours. If high in response to infection it dropped steadily as the infection was controlled, but never below normal limits. The leucocyte count should therefore come into prominence as an indication of progress, in treatment by penicillin, where the temperature chart often does not reflect improvement in the early stages.

c. Accessibility of thecal and serous cavities. Passage of penicillin between the blood stream and serous cavities seems

to be slight (Rammelkamp & Keefer, 1943a, 1943b; Fleming, 1943; Florey, M. E. & Florey, H. W., 1943), and for treatment of infections of the meninges, pleural cavity, joints and peritoneum local rather than intramuscular or intravenous injection is therefore indicated. The physiological basis of the apparent (relative) impermeability of these membranes to penicillin still remains to be elucidated.

d. Toxicity. Any signs of toxicity have been carefully sought by observation of the patient, by regular examinations of blood urea and urine, and by hæmatological examinations. Occasionally the blood urea has risen but it has fallen again on the day on which penicillin has been discontinued. No case in which albuminuria has developed has been recorded in the English series, but when present initially it has cleared up under penicillin therapy. Fever often increases when penicillin is first administered, but gradually subsides again. This rise of temperature may be due to a more rapid absorption of bacterial degradation products rather than to any toxic effect of the drug.

e. Radiological findings. Special mention should be made of the radiological appearances of infected bone treated with penicillin. A very rapid rarefaction of the affected bone occurs, and radiography in less than a week, often in 2 or 3 days, suggests deterioration, whereas the clinical signs indicate that the septic process is under control. Further radiographs demonstrate the rapid reformation of bony tissue as compared with control cases, in which (in the series of hand infections) sequestrum formation occurred more often than not. In acute infections no sequestrum formation has been found in the English penicillin-treated series. If, in a chronic infection, dead bone has already separated before the beginning of penicillin treatment, rare-

FIG. IV—A case of osteomyelitis with pyæmia in a male child of 8. The child received just under 2,000,000 units of penicillin intramuscularly.

(a) Right tibia and fibula before penicillin treatment was begun.

(b) Three weeks later, at the conclusion of penicillin treatment.

The characteristic rarefaction which occurs in infected bone during penicillin treatment is well illustrated. The boy, who had been desperately ill, made a good recovery without surgical intervention.

Photograph reproduced from the *Lancet*.



(a)

(b)

faction will occur around the sequestrum and will make its presence and site more obvious to the surgeon.

f. Bacteriological desiderata.

Mention of the organisms sensitive to penicillin has been made elsewhere (Fleming, 1929; Abraham *et al.*, 1941). It is clearly futile to attempt penicillin treatment when the organism concerned is insensitive. Emphasis has already been laid on the speed and completeness with which organisms usually disappear during treatment with penicillin. A few further points, however, should be borne in mind. Bacteria do not readily disappear from lesions if there is any dead tissue present such as a slough or sequestrum, nor do they disappear when access by the drug is not complete. This may occur with systemic treatment in undrained abscess cavities or in serous cavities, where the penicillin may be brought by the blood stream only as far as the periphery of the infected area. It may also occur with local treatment in sinuses which have not been completely opened up, or in septic areas where the incision has not reached the whole site of infection. Disappearance and elimination of infection, therefore, depend on (a) a sensitive organism, (b) adequate dosage, (c) absence of dead tissue, (d) full access to the site of infection. It has not been uncommon to find coliform organisms appearing or increasing in number during penicillin administration, but they do not appear to affect the clinical course or delay healing materially, even when green or pinkish "gram-negative pus" is present.

In vitro, bacteria readily become penicillin-resistant, and some clinical cases have been reported where resistance of the order of 4 to 8 times developed during treatment although clinical improvement continued (Florey & Florey, 1943; Rammelkamp & Maxon, 1942). Sulphonamide-resistant strains have been found, however, to be fully sensitive to penicillin.

Methods of Treatment

a. Systemic administration. In the early clinical trials the greatest difficulty encountered was to find the adequate dosage. The ring test (Abraham *et al*, 1941) was not sufficiently sensitive to demonstrate any bacteriostatic effect in the blood after doses which were believed on theoretical grounds to be large enough to produce bacteriostasis throughout the body. Eventually, after trial and error, a baby provided the foundation on which an adequate dose to eliminate infection was established as 1,000 units per pound [454 g.] of body weight in 24 hours. Later, the more delicate slide-cell technique was adopted, in which the inhibition of bacterial growth by the blood serum could be accurately followed. This served to establish that intravenous or intramuscular injection should be repeated not less than 3-hourly, the standard single dose for an adult being 15,000 Oxford units. Later work by Rammelkamp & Keefer (1943b) has shown that even when nearly 3 times the dose is given there is no prolongation of the time during which the drug can be detected in the blood stream. Good effects have been produced in acute infective conditions by much smaller doses than 15,000 units in the Mayo Clinic (Herrell, Heilman & Williams, 1942; Herrell, 1943) and elsewhere, but although these results are very satisfactory it would seem wise for general use to recommend a dosage which has been found adequate in many conditions—acute, well-established, or long-standing—especially in view of the fact that organisms may become penicillin-resistant.

The *gastro-intestinal* route was tried—by mouth in specially prepared capsules to resist solution by the acid gastric juice, and by duodenal tube. Although some absorption certainly took place, the variable rate at which the drug was absorbed rendered the bacteriostatic concentration in the blood inconstant and uncertain when doses of a size which is at present practicable were used.

In the early clinical work, *subcutaneous* injection was avoided owing to the pain associated with it. Although according to the work of Rammelkamp & Keefer (1943b) there may be some advantage in using this route, as an adequate blood level is apparently maintained for longer than after intramuscular or intravenous injection, the large volume of fluid used was inconvenient and may explain the slow absorption.

For the best results by *intravenous* use it is essential to use a pyrogen-free preparation (the pyrogenic impurity can be removed during purification). The penicillin may be given intermittently, or continuously by a "drip" infusion. Thrombosis at the site of injection is common after a variable period of intravenous therapy, although with good samples of the drug the "drip" can often be continued for some days.

For this and other reasons the *intramuscular* route was adopted for general use in the British work. Providing a good technique is used, most samples cause little general or local reaction, but some samples have been encountered which do cause prolonged pain after intramuscular injection. There can be little doubt that this reaction, the thrombosis after intravenous injection, and other reactions of a minor character are due to impurities. As the penicillin used therapeutically is still far from pure, usually containing only 10–20% of the pure substance, it is to be hoped that the quality of penicillin produced for clinical purposes will improve. By the use of the intramuscular route, material which causes a sharp rise of temperature on intravenous administration can be employed without causing a pyrexial reaction.

b. Local administration has been used extensively in Britain, largely because of the scarcity of supplies, but many instances might be given where it has advantages over systemic treatment. Where an infection is definitely localised, and there is a surface or cavity which will retain a preparation of penicillin, a much greater concentration can be applied to the site of infection and, by using a suitable vehicle, the action of a single dose may be prolonged for as long as

24 hours. For this purpose the following preparations have been found useful:

- i. A dry calcium-penicillin powder of low potency (i.e. a relatively unpurified preparation containing a low percentage of pure penicillin).
- ii. A powder composed of a calcium-penicillin preparation diluted with sulphanilamide or sulphathiazole powder to a strength of 2,000 to 5,000 units of penicillin per gram. Such a powder is very suitable for insufflation.
- iii. Solutions in distilled water of 250 to 1,000 units per cm.³
- iv. A paste made up of lanette wax SX, oil (e.g. castor or arachis) and water to which penicillin is added to a strength of 150 to 250 units per cm.³ With this preparation the activity of the drug may be retained for at least 24 hours.
- v. Mixed with vaseline or some other base as an eye ointment—500–800 units per cm.³

Various methods of local application have been used, such as simple dressings impregnated with the paste preparation, insufflation of powder, or spreading of the powders over infected surfaces. A method which, when applicable, is very effective because it embodies the principle of maintaining a closed cavity, is to aspirate pus and inject a solution by syringe and needle. An alternative method is to remove the purulent and damaged tissue from an abscess cavity or wound, suture the raw edges and insert one or more narrow rubber tubes (retaining them by a suture) leading down to the depths of the cavity. In the latter method, the cavity is aspirated and the penicillin solution is injected through the tubes by means of a syringe. One extremity of the tube projects through the dressings. Injections are made 6- to 12-hourly according to the acuteness of the condition, for a minimum period of 5 days.

Sinuses of many years' duration have been treated successfully by injection of the solution under pressure, thereby opening up their many ramifications. The mouth of the sinus is closed with a sterilised rubber bung in order to retain the fluid from one injection until the next. This retention of the drug continuously *in situ* over a period of time has been a cardinal feature of treatment. Because of its bacteriostatic rather than bactericidal action, time must be allowed for the inhibited bacteria to perish by phagocytosis or otherwise. Any temporary cessation of the inhibitory influence of penicillin may permit further bacterial proliferation and so prolong the time necessary to eliminate infection.

The duration of treatment has depended on the time taken to eliminate bacteria from lesions. There is no indication that increased dosage beyond the point necessary to secure complete bacteriostasis is of any value. The effect of higher dosage is merely to cause more rapid excretion of the drug by the kidneys. Bearing in mind the possibility that the pathogenic organisms may develop resistance to penicillin, a fully bacteriostatic dose should be given from the beginning. There has been little evidence, except in subacute bacterial endocarditis, that an infection by a sensitive organism will not respond to prolonged treatment. The point to be remembered is that treatment must be continued until all foci of infection have been removed. As mentioned earlier, when dead tissue is present, surgical removal may be necessary, but radiological and bacteriological findings are better indications for this than is the temperature chart.

Assessment of Progress

a. General infections. When treating a case with penicillin, assessment of progress is liable to be based on the signs familiar in sulphonamide therapy. This may, unfortunately, lead to erroneous conclusions. The temperature, for instance, in a case of osteomyelitis may assume a swinging character when penicillin is first given, and it never falls rapidly, as often occurs with the sulphonamides. Often the temperature mounts to a higher level than before treatment was instituted.

By the time the temperature has become normal, which may take from 2 to 3 weeks, resolution has largely taken place. The radiograph, which in infections of bone shows rapid and often startling rarefaction, should be regarded as evidence of the fast absorption of damaged bony tissue, and not of deterioration in the condition.

The earliest signs of progress are noticed by the nursing staff. Within a day or two the patient sleeps better, eats better and is relieved of much pain. Bacteriological examina-

tion carried out twice a week will reveal steady diminution and eventually total disappearance of the infecting organism, provided that the drug has full access, locally or systemically, to the whole of the infected part, and that there is no dead tissue remaining to form a nidus for the infection.

If there is no diminution of bacterial growth within a week, consideration must be given to the advisability of aspiration or surgical interference in order to gain better access to localised lesions.

The blood count is also of value in assessing the arrest of infection. A steady fall of the leucocyte count to within normal limits and a rise in the erythrocyte count are indications that good progress is being made.

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¹ [see BMB 212]

² [see BMB 238]

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⁵ [see BMB 236]

⁶ [see BMB 233]

³ [see BMB 234]

⁴ [see BMB 203]

⁷ [see BMB 237]

[All other references are to be found among those given in BMB 242]

REVIEW OF SELECTED PAPERS

Discovery: Early Investigations: Bacteriological Applications

In this section are described the first investigations on penicillin, and the early and later application of its selective bacteriostatic properties in bacteriological techniques. The work which led to the effective application of penicillin in the treatment of bacterial infections is described in another section.

203

ON THE ANTIBACTERIAL ACTION OF CULTURES OF A *PENICILLIUM* WITH SPECIAL REFERENCE TO THEIR USE IN THE ISOLATION OF *B. INFLUENZAE* by A. Fleming, *British Journal of Experimental Pathology*, 10, 226-236, June 1929

In this paper, published in 1929, Professor Alexander Fleming, of St. Mary's Hospital, London, first described his discovery of penicillin and the investigations by which he established certain important facts about the substance.

"While working with staphylococcus variants a number of culture-plates were set aside on the laboratory bench and examined from time to time. In the examinations these plates were necessarily exposed to the air and they became contaminated with various micro-organisms. It was noticed that around a large colony of a contaminating mould the staphylococcus colonies became transparent and were obviously undergoing lysis."

It was evident that a substance antagonistic to the bacteria had been formed by the mould and had diffused into the surrounding agar. He therefore subcultured the mould for further study and found that broth in which it had grown for a week or two acquired marked inhibitory properties to many common bacteria.

Characteristics of the mould. On a solid medium [composition not stated] a colony of the mould, in Professor Fleming's own words, "appears as a white fluffy mass which rapidly increases in size and after a few days sporulates, the centre becoming dark green and later in old cultures . . . almost black. In 4 or 5 days a bright yellow colour is produced which diffuses into the medium. In certain conditions a reddish colour can be observed in the growth. In broth the mould grows on the surface as a white fluffy growth changing in a few days to a dark green felted mass. The broth becomes bright yellow." The reaction of the medium became alkali-

line, pH 8.5 to 9. Growth was slow at 37° C., and most rapid at about 20° C. No growth took place anaerobically. Other moulds of several species were tested, including 8 other strains of penicillium, but only one, which was apparently identical with the original strain, produced any inhibitory substance. The active strain resembled *Penicillium rubrum* [but was later identified as *Penicillium notatum* (Fleming, 1932).]

Tests of activity. The antibacterial activity of the broth was tested in two ways: (i) A strip was cut out of an agar plate and the resulting gutter was filled with agar mixed with an equal amount of the broth. The bacteria to be tested were streaked across from the gutter to the edge of the plate. The active substance diffused from the gutter into the surrounding agar, where it inhibited the growth of susceptible organisms. (ii) Serial dilutions of the active broth were made in plain broth and the tubes were inoculated with equal amounts of bacterial culture. The staphylococcus was found to be a suitable organism for testing the activity of the broth, as it was very sensitive. It was not necessary to filter the broth before testing, as no appreciable growth of the mould took place in 24 hours at 37° C.

Development of the active substance. When 200 cm.³ of nutrient broth in a 500 cm.³ Erlenmeyer flask was inoculated with mould spores and incubated at 20° C. it gradually developed antibacterial activity until at 7 or 8 days it would inhibit the growth of staphylococci when diluted 1:500 or 1:800. On keeping longer, the activity diminished. The droplets of fluid which formed on the surface of the mould had a higher titre than the broth, sometimes as great as 1:20,000.

The filtered broth lost activity in a few days, but was more stable if the pH was adjusted to 6.8. Heating for an hour at 56° or 80° C. and boiling for a few minutes did not destroy the activity, but boiling for an hour reduced it and autoclaving for 20 minutes at 115° C. abolished it. Boiling was less destructive if the broth was first neutralised. The active substance was soluble in water and saline and was not removed by Seitz filtration.

Antibacterial tests. In a long series of dilution tests, it was shown that some species of bacteria were inhibited by the broth in dilutions up to 1:800, while others, relatively insensitive, were not inhibited by a dilution of 1:5. Staphylococcus (*aureus* and *epidermidis*), streptococcus and pneumococcus were the most sensitive and *B. coli*, *B. typhosus*, *Ps. pyocyanea*, *B. proteus*, *V. cholerae* and *Strept. faecalis* the

least. *B. diphtheriae* and *B. anthracis* occupied an intermediate position. Different strains of *Strept. viridans* varied widely in sensitivity. *B. pseudotuberculosis rodentium*, *B. pullorum* and *B. dysenteriae* were as insensitive as the colityphoid group. These results were confirmed by the gutter test, by which also the meningococcus and gonococcus were shown to be as sensitive as the staphylococcus, and *H. influenzae* to be insensitive. The original mould was not inhibited by the broth. It was shown that staphylococci were not suddenly killed but disappeared gradually over some hours, when in contact with penicillin.

Toxicity. The active broth was shown to be no more toxic than plain broth when given intravenously to rabbits and mice, and to cause no irritation or other undesirable effect when applied to the conjunctiva and to large ulcerated areas in man. A concentration which completely inhibited the growth of staphylococci did not disturb the normal function of leucocytes more than plain broth.

Use in bacteriology. It was shown in various ways that penicillin broth suppressed the growth of staphylococci and streptococci on an agar plate, while allowing the development of insensitive organisms from a mixed culture. For the isolation of *H. influenzae* (Pfeiffer) its use was particularly recommended. The penicillin broth could be incorporated in the agar or, more simply, it could be spread over half the plate after inoculation. Boiled blood agar was recommended as a medium. In 25 clinical cases of "influenza" the bacillus grew from the throat swab of 23 with the aid of penicillin broth and from only 8 without the penicillin.

In his discussion the author points out that his penicillin broth inhibited sensitive organisms at a higher dilution than carbolic acid or other chemical antiseptics in common use. It was in addition non-irritant and non-toxic. Experiments to investigate its value in treating pyogenic infections were in progress. In addition to its possible clinical use, it was certainly useful in bacteriology, notably in facilitating the isolation of *H. influenzae*.

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¹ Fleming, A. (1932) *J. Path. Bact.* 35, 831

¹ [see BMB 205]

104

ON THE OCCURRENCE OF INFLUENZA BACILLI IN THE MOUTHS OF NORMAL PEOPLE

by A. Fleming & I. H. Maclean, *British Journal of Experimental Pathology*, 11, 127-134, April 1930

In the work here reported Professor Fleming and Dr. Maclean, of the Inoculation Department, St. Mary's Hospital, London, investigated the mouths of normal people for the presence of hæmoglobinophilic bacilli (*H. influenzae* (Pfeiffer) and related organisms). Previous workers had reported finding such organisms in between 25 % and 80 % of normal subjects. In the present work they were found in all of 36 mouths, and usually in several situations, i.e. gum, tonsil and post-nasal space. The strains isolated were very variable as regards their cultural characters. In 6 mouths studied with especial care both influenza and para-influenza strains were isolated from the gums in every case, and in the rest para-influenza bacilli were always found in the gums. The success of their work was attributed by the authors to the use of penicillin for differential culture, since in a suitable concentration it suppressed the growth of the gram-positive cocci and *M. catarrhalis*, while allowing the growth of the influenza group of bacilli.

The filtrate from a culture of *Penicillium notatum* could be used in three ways :

i. The infected material was spread on an agar plate and then half the plate was spread with 4 to 8 drops of penicillin broth. This simple method produced a plate, half of which showed a complete culture and half a differential culture.

ii. A more exact method was to make several dilutions of the penicillin broth in a suitable fluid medium and inoculate all the tubes with infected material. The influenza bacillus was at least 40 times less sensitive than the staphylococcus, so that if, for example, the staphylococcus was inhibited at 1:400, suitable dilutions for isolating influenza bacilli would be 1:3, 1:6, and 1:10. After 24 or 48 hours' incubation the cultures were plated out.

iii. Plates were made with a solid medium in which penicillin broth was incorporated in known dilutions.

These methods enabled the authors to isolate influenza bacilli when, on ordinary culture, they would have been overgrown or inhibited by other organisms.

205

ON THE SPECIFIC ANTIBACTERIAL PROPERTIES OF PENICILLIN AND POTASSIUM TELLURITE

by A. Fleming, *Journal of Pathology and Bacteriology*, 35, 831-842, November 1932

In this paper the author recalls the discovery of penicillin (Fleming, 1929) and describes its use in bacteriology. He also reports on its first use as a dressing on septic wounds.

When his strain of *Penicillium notatum* was grown in trypsin digest broth for 6 or 7 days at 20° C. the filtered broth completely inhibited the growth of staphylococci when diluted 1:800. The broth, which was alkaline, sometimes preserved its potency for as much as 3 months, if neutralised to about pH 6.8 and subsequently adjusted when necessary.

By incorporating this penicillin broth in culture media, bacteria could be divided into two broad groups: (a) those whose growth was prevented by concentrations of 1 % or less, and (b) those which would grow even in the presence of a 5 or 10 % concentration. The methods of using the penicillin broth in culture media were the same as those described by Fleming & Maclean (1930).

After describing the use of potassium tellurite in bacteriology (dilutions of 1:1,000 spread on a plate, or 1:20,000 incorporated in the medium where suitable), the author gives a table showing penicillin and tellurite to be complementary, the organisms sensitive to one being insensitive to the other and *vice versa*. Exceptions were the enterococci, moulds and yeasts, and some types of *B. coli* and *B. proteus*, which were sensitive to neither, and the gonococcus which was sensitive to both.

Examples of the Use of Penicillin

i. To isolate the hæmophilic bacteria, which are penicillin-insensitive, from mixed cultures [see Fleming & Maclean, 1930].

ii. To isolate the acne bacillus, which is only moderately sensitive, from material in which it is mixed with the staphylococcus, which is highly sensitive [see Craddock, 1942].

iii. To distinguish the saprophytic gram-negative cocci (such as *M. flavus*), which are insensitive, from the pathogenic gram-negative cocci which are highly sensitive.

iv. To demonstrate the inhibition of one bacterial species by another. For example, a plate was sown with a mixed culture of a streptococcus and *V. cholerae*, and penicillin was spread over half the plate. In the presence of penicillin the streptococcus did not grow, and a pure culture of *V. cholerae* was found. On the other half of the plate the streptococcus suppressed the growth of the vibrio and was itself found in pure culture. Many similar examples are given.

v. In combination with potassium tellurite, to isolate one species of bacterium from a mixture. For example, sputum was cultured in broth containing a high concentration of penicillin and a low concentration of tellurite. The penicillin inhibited the growth of the gram-positive cocci, while the tellurite inhibited para-influenza bacilli and other gram-negative organisms. *H. influenzae*, which is slightly less sensitive to tellurite than the para-influenza organisms, grew out in pure culture.

vi. As a dressing for septic wounds. The penicillin-containing broth, which appeared perfectly harmless, had been used to dress a number of indolent septic wounds, and had "certainly appeared to be superior to dressings containing potent chemicals." The author believed that it did not act by killing the bacteria directly. Its use as a dressing presented certain difficulties, because of the labour of preparation and the instability of the active principle.

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¹ Craddock, S. (1942) *Lancet*, 1, 558

² Fleming, A. (1929) *Brit. J. exp. Path.* 10, 226

³ Fleming, A., & Maclean, I. H. (1930) *Brit. J. exp. Path.* 11, 127

¹ [see BMB 208]

² [see BMB 203]

³ [see BMB 204]

THE FORMATION FROM GLUCOSE BY MEMBERS OF THE *PENICILLIUM CHRYSOGENUM* SERIES OF A PIGMENT, AN ALKALI-SOLUBLE PROTEIN AND PENICILLIN—THE ANTIBACTERIAL SUBSTANCE OF FLEMING

by P. W. Clutterbuck, R. Lovell & H. Raistrick, *Biochemical Journal*, 26, 1907–1918, 1932

Professor Raistrick and his co-workers at the *London School of Hygiene & Tropical Medicine*, University of London, followed up Fleming's original discovery by initiating chemical investigations on penicillin. In this paper they describe the production of penicillin by Fleming's mould in a synthetic medium, and preliminary attempts to isolate the antibacterial substance. [A yellow pigment, chrysogenin, and an alkali-soluble protein were also found in the metabolism solution, but these will not be discussed here.]

Fleming's mould was reported by Dr. Charles Thom to be closely related to *P. notatum* Westling in the *P. chrysogenum* Thom series. The organism was grown in conical flasks on a modified Czapek-Dox medium of the following composition:

NaNO ₃	3.0 g.
KH ₂ PO ₄	1.0 g.
KCl	0.5 g.
MgSO ₄ .7H ₂ O	0.5 g.
FeSO ₄ .7H ₂ O	0.01 g.
Glucose	40.0 g.
Distilled water	to 1 litre

The temperature of incubation was 25° C. At the end of a period of incubation the metabolism solution was sterilised by passing it through a Seitz filter. Its antibacterial power was then determined by inoculating one loopful of the test organism into tubes containing varying dilutions of the filtrate in trypsinised horse-muscle broth. After incubation at 37° C. for 24 hours, opacity readings were taken.

The antibacterial substance was found to reach its maximum concentration at about the 16th to 20th day, when the metabolism fluid inhibited the growth of *Strept. pneumoniae* at a dilution of 1:1,280. Further incubation resulted in a loss of activity.

Penicillin was found to be quickly inactivated by evaporation *in vacuo* at 40° C. in both acid and alkaline solutions, but it was moderately stable at pH 3.6, which caused the flocculation of most of the protein and chrysogenin. The filtrate was then adjusted to pH 5.5 and concentrated *in vacuo*. This resulted in a partial loss of activity. At pH 2 (but not at pH 7.2) the active substance could be extracted by ether. Evaporation of the ethereal extract to dryness gave an inactive residue, but evaporation *in vacuo* over water left an aqueous solution which, after adjusting to pH 7.2, still contained some of the original activity.

207 A MODIFICATION OF THE COUGH PLATE METHOD OF DIAGNOSIS IN WHOOPING COUGH

by I. H. Maclean, *Journal of Pathology and Bacteriology*, 45, 472–473, September 1937

The author recommends the use of penicillin as an aid to isolating *H. pertussis*. A few drops of broth from a culture of *Penicillium notatum* were spread over one-half of 50 "cough plates"; 47 were positive on the penicillin side and only 33 on the untreated side. Swabs taken from the pharynx just after coughing and planted on similar plates gave 75–80% positive results with penicillin and about 10% without. By both methods the use of penicillin allowed a heavier inoculum, as the number of colonies of streptococci and staphylococci was greatly reduced.

208 USE OF PENICILLIN IN CULTIVATION OF THE ACNE BACILLUS

by S. Craddock, *Lancet*, 1, 558–559, 9/5/42

The author, working in the Inoculation Department of St. Mary's Hospital, states that in acne lesions the acne bacillus is usually accompanied by *Staph. albus*, but that by the use of penicillin pure cultures could be obtained.

Method. A tube of glucose broth (pH 6.8) was boiled to expel dissolved gases. When cool, pus from an acne lesion was inoculated into it. The filtrate from a culture of *Penicillium notatum* was added, diluted so that the broth finally contained a concentration of penicillin twice as great as that needed to prevent the growth of staphylococci (this concentration was determined by a preliminary titration). Hot sterile "vaseline" [petroleum jelly] was run on to the surface to a depth of 0.5–1.0 cm., and the tube was incubated at 37° C. After about 60 hours a growth of the bacillus was visible and after 4 days it was abundant.

By this method the bacillus was isolated in pure culture from all of 47 specimens of material from acne pustules, comedones and sebum, though without penicillin 34 grew staphylococci in addition.

Chemotherapeutic Action: Pharmacology: Bacteriological Investigations

Under this heading is described the first successful use of penicillin as a chemotherapeutic drug in experimental animal infections, which was made possible by the extraction of active, although still impure, material from the crude penicillin-containing fluid. Preliminary observations on the pharmacology of the drug were made. This work provided evidence that penicillin might have important therapeutic possibilities. A bacterial enzyme which destroys penicillin, and the morphological effects of penicillin on bacteria, are also reported.

209

PENICILLIN AS A CHEMOTHERAPEUTIC AGENT

by E. Chain, H. W. Florey, A. D. Gardner, N. G. Heatley, M. A. Jennings, J. Orr-Ewing & A. G. Sanders, *Lancet*, 2, 226–228, 24/8/40

In this, the first paper on penicillin by the Oxford workers, Professor Florey and his collaborators describe how, following up some work on lysozyme, "it occurred to two of them [Dr. Chain and Professor Florey] that it would be profitable to conduct a systematic investigation of the chemical and biological properties of the antibacterial substances produced by bacteria and moulds." One such substance was penicillin, which had been discovered, named and described by Fleming in 1929. It was produced by a mould of the species *Penicillium notatum* and had promising antibacterial properties.

Methods of culture, assay and extraction of penicillin were not described in this paper, the authors confining themselves to reporting their first antibacterial, toxicity and therapeutic tests. The tests were carried out with crude penicillin in the form of a brown powder, freely soluble in water, prepared from the culture medium. [It is now known that this powder contained only from 1% to 2% of pure penicillin.]

Antibacterial action in vitro. A number of pathogenic bacteria were tested and found to be inhibited by dilutions of one in several hundred thousand, i.e. *Cl. welchii*, *Cl. septicum*, *Cl. oedematiens*, *C. diphtheriae*, *Sirept. pyogenes*, *Sirept. viridans*, *Strept. pneumoniae* and staphylococcus. Penicillin appeared not to be bactericidal, but to interfere with multiplication of the bacteria.

Toxicity. Ten mg. intravenously had no apparent ill effect on a mouse weighing 23 g. Larger doses, 10 mg. 3-hourly for 56 hours, given subcutaneously to two rats, had no general effect, though there appeared to be a transient decrease in the polymorph count and some histological evidence of damage to the renal tubules. In a cat, 40 mg. intravenously (representing a blood concentration of 1:5,000) did not alter the blood pressure, heart beat or respiration. An isolated cat's heart slowed during the perfusion of 1:5,000 and 1:10,000 solutions, but recovered as soon as perfusion with penicillin was stopped. Human leucocytes remained active in a 1:1,000 solution.

Absorption and excretion. Penicillin in solution was absorbed from the intestine of the rat without damage to the mucosa, and from the subcutaneous tissues, and was excreted by the kidneys. It was present in the blood and was excreted in the urine, which it coloured bright yellow.

Therapeutic effect. Five therapeutic experiments were performed, two with *Strept. pyogenes*, two with *Staph. aureus* and one with *Cl. septicum*. The first two were injected intraperitoneally and the last, as a spore suspension with 2.5 % calcium chloride, intramuscularly. Penicillin was given by subcutaneous injection, 3-hourly for the first 3 days and then at longer intervals. In the first experiment with streptococci, where treatment was only continued for 12 hours, life was prolonged, but at 10 days 25 out of 50 treated mice were dead, compared with 21 out of 25 controls. In the next experiment a smaller total dose was given—7.5 instead of 10 mg.—but it was spread over 45 hours; 24 out of 25 treated mice survived, whereas all the controls (25) were dead in 16 hours. A similar result was obtained with *Staph. aureus*. In the first experiment treatment was inadequate, though continued for 55 hours, but when it was continued for 4 days, 21 out of 24 mice survived, whereas all the controls were dead in 48 hours. The *Cl. septicum* infection killed the 25 controls in 17 hours, but after treatment, which lasted 10 days, 24 out of 25 mice receiving a total of 38 mg., and 18 out of 25 receiving half that dose, survived. It was noticed that the mice infected with streptococci and staphylococci looked gravely ill for the first few hours, even when undergoing treatment, but thereafter recovered and were normal in 36 to 48 hours.

210

AN ENZYME FROM BACTERIA ABLE TO DESTROY PENICILLIN

by E. P. Abraham & E. Chain, *Nature*, 146, 837, 28/12/40

Though *B. coli* was insensitive to the antibacterial power of penicillin, no inactivator of penicillin was found in the culture fluid. The possibility remained that the bacterial bodies themselves contained an inactivating substance. A suspension of the bacilli was ground up in a bacterial crushing mill and the resulting bacterial extract was found to inactivate penicillin completely. The inhibitory substance had the properties of an enzyme, and the authors named it "penicillinase." The inactivation took place with equal readiness under aerobic or anaerobic conditions; there was no uptake of oxygen or appearance of acid groups during the reaction.

The enzyme was not found in *Staph. aureus* but was present in *M. lysodeikticus* which was sensitive to penicillin, though less so than the staphylococcus. It was absent from yeast and from *Penicillium notatum*. An air bacterium, a gram-positive rod, also contained the enzyme, and in this case it was present also in the culture fluid.

211

MORPHOLOGICAL EFFECTS OF PENICILLIN ON BACTERIA

by A. D. Gardner, *Nature*, 146, 837-838, 28/12/40

The author, Professor in Bacteriology in the University of Oxford, reports that penicillin altered the morphology of bacteria when present in concentrations too small to inhibit growth completely. The effect could be seen at concentrations down to a 10th, and in some cases even a 30th, of that needed for complete inhibition.

The principal changes appeared to be due to incomplete division, giving rise to swollen and grotesque giant forms and, in the case of bacilli and vibrios, to long filaments. Such forms would presumably be abnormally vulnerable to leucocytes and other defence mechanisms, and penicillin might therefore be expected to have an effect *in vivo* at concentrations too low for complete bacteriostasis.

First Clinical Trials: Production: Biological Properties

In the single comprehensive paper reviewed under this heading is reported the successful application, in the treatment of human infections in a small number of cases, of the data obtained by laboratory experiments. Large-scale laboratory production was described, but material was still very scarce. The work reported in the previous year was considerably amplified. Steps towards the purification of penicillin were made.

FURTHER OBSERVATIONS ON PENICILLIN

by E. P. Abraham, E. Chain, C. M. Fletcher, H. W. Florey, A. D. Gardner, N. G. Heatley & M. A. Jennings, *Lancet*, 2, 177-188, 16/8/41

This paper embodies the full account of the first investigations by the Oxford workers. It includes details of the growth of *Penicillium notatum* and laboratory large-scale production; the methods of assay of the active substance; chemical methods for extraction and purification of penicillin; a fuller investigation of its bacteriostatic action and toxicity, and of absorption and excretion; and finally a report of the first therapeutic trials on man.

[It should be noted that the penicillin preparations used in the work here described contained varying amounts of the pure substance and never more than 5 %. The paper is therefore more valuable for its description of the properties of penicillin than for the quantitative data it contains.]

Growth of the Mould

For the production of penicillin, the mould was grown on the modified Czapek-Dox medium of Clutterbuck *et al.* (1932), with tap water instead of distilled water; 10 % of yeast extract was added, or 2 % if the medium was being placed under mould already grown. [Other media producing a higher yield of penicillin are now in use, but the formulae are as yet unpublished.]

When a spore suspension of *Penicillium notatum* was sown into this medium and incubated at 24° C., the mycelium developed, remaining submerged for 3 days and then reaching the surface (the depth of the fluid being 1 cm.), where it formed a continuous mat. If the medium was disturbed even by gentle rocking, formation of the mat was delayed. By the 6th or 7th day the mat was corrugated and covered by bluish-green spores, sometimes with yellow droplets lying on the surface.

The pH of the medium fell until the 3rd day and then rose to over pH 8. Penicillin production was maximal at about pH 7. Various conditions affecting growth were noted, and the need for strict sterility was emphasized, as certain bacteria destroyed penicillin. For maximum production the depth of the medium did not exceed 1.5 to 2 cm.

Method of Assay

A method was devised by which the antibacterial activity of solutions could be rapidly tested. Glass or vitreous porcelain cylinders 9.6 mm. long and of 5.1 mm. internal diameter, at the lower end internally bevelled and ground flat, are placed on the surface of an agar plate which has been uniformly sown with a broth culture of *Staph. aureus* and dried. The ground end makes a water- and bacteria-tight junction with the agar, so that non-sterile fluids can be placed in the cylinder for testing without contaminating the agar plate. [It has since been found advantageous to heat the cylinder for a moment before placing it on the agar.] The active substance diffuses from the fluid into the agar and inhibits the growth of the staphylococcus round the cylinder for a distance proportional to its concentration in the fluid. Several samples can be tested on one plate.

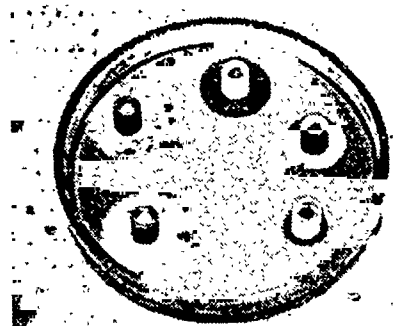


FIG. V.—The plate and cylinder ring test devised by N. G. Heatley and described above.

Reproduced by permission of *Endeavour*.

Various points affecting the use of the cylinders are discussed. Tests done in triplicate with solutions so diluted as to produce a ring of inhibition not more than 25 mm. in diameter have probably an error of not more than ± 25 % and possibly much less. A standard penicillin solution should be included on every plate for comparison.

Laboratory Large-Scale Production

The mould was grown in closed rectangular porcelain vessels, 27.5 × 22 × 6 cm. external diameter, with a side arm for filling and inoculation. The medium, enough to fill the vessels to a depth of 1.7 cm., was sterilized in the vessels, inoculated with a few drops of spore suspension and incubated at 24° C. An apparatus for withdrawing and replacing the medium under the mat of mould is described in detail.

Extraction from the Medium

Some details of the method of extraction are given, which rest upon the following general principle. At pH 2 the active substance will pass from aqueous solution into ether, amyl acetate, and certain other organic solvents. As, however, in aqueous solution it is rapidly destroyed at this pH at room temperature, the extraction must be carried out rapidly or in the cold. It passes back into aqueous solution at pH 6-7. The substance obtained as a sodium salt preparation after a single extraction of this type was found to be pyrogenic for rabbits and man. For further purification it was passed in ethereal solution through a chromatographic adsorption column of Brockmann's alumina. The final product, the sodium salt in aqueous solution, was a deep reddish-orange, yellow when diluted, and had a faint characteristic smell and a bitter taste. It was suitable unmodified for therapeutic injection, after blowing off the ether, or it could be dried, yielding a voluminous hygroscopic yellow powder, and redissolved when required. [Extraction based on these principles is still in general use for industrial production.]

Antibacterial Action

The purest preparation available at the time of writing inhibited several species of bacteria, including *Staph. aureus* at a dilution of 1:1,000,000 and the gonococcus at 1:2,000,000. The work of Fleming (1929) on the susceptibility of different bacterial species was, in general, confirmed. In addition, the clostridia were found to be highly sensitive, *S. gaertneri* and *S. typhi* to be of intermediate sensitivity, and *Myc. tuberculosis* to be insensitive.

A staphylococcus when repeatedly subcultured in medium containing penicillin became rapidly resistant—eventually 1,000 times less sensitive. It was shown that this acquired resistance was not due to an enzyme which destroyed penicillin.

Penicillin was shown to be, like the sulphonamides, bacteriostatic not bactericidal. It differed in its antibacterial action from the sulphonamides in the following ways:

- i. It was active at a much higher dilution.
- ii. It was little affected by the number of bacteria present.
- iii. It was not inhibited by serum, blood, pus, autolysed tissues or peptones.

Toxicity to Tissue Cells

Humc. leucocytes adhering to a coverslip were inverted over a well-slide containing penicillin dissolved in a special physiological saline with 10% of serum. The leucocytes were watched under the microscope for 4 hours. In 1:100 penicillin they died immediately, but in 1:500 they were indistinguishable from control preparations. By comparison, proflavine killed immediately at 1:20,000, and 2:7 diamino-acridine-monohydrochloride and sodium hypochlorite at 1:10,000. The sulphonamides were by this test little more toxic than penicillin, as the leucocytes, though they became inactive, survived for 2 hours or more in 1:500 sulphanilamide and in saturated solutions of sulphapyridine and sulphathiazole. [Purer preparations of penicillin have since been shown to be less toxic to leucocytes than these (Florey & Jennings, 1942).]

In *tissue culture* it was shown that there was no difference between fibroblasts and epithelial tissues in respect of their sensitivity to penicillin; the smallest concentration at which any toxic effect was seen was about 1:5,000. Fibroblasts exposed to a 1:1,600 solution for 48 hours began to grow again when the drug was removed, and hen's blood macrophages similarly recovered after 42 hours in a 1:200 solution.

The *central nervous system* was the site chosen for an experiment on local application. A 1:1,000 solution of penicillin was made to flow into the cerebrospinal space of two rabbits through a cisternal puncture by slowly injecting

11 cm.³ of 25% sodium chloride intravenously. In one rabbit 2.0 cm.³ of penicillin solution was drawn in and in the other 1.5 cm.³ Neither showed any disturbance, and histological examination 6 days later was completely negative. Examination of the cortex of other rabbits to which penicillin had been applied directly was also negative.

Absorption and Excretion

These were investigated in the cat, the rabbit and man. It was shown in the cat that penicillin was absorbed from the subcutaneous tissues and from the intestine. It could be detected in the blood for at least 1 hour after subcutaneous or intravenous injection, and for at least 3 hours after intestinal administration. It was present in the urine for 6 hours or more and was excreted in high concentration in the bile, where it reached its maximum at 3 or 4 hours. After intravenous injection, the saliva contained a trace, but none could be detected in the tears, the pancreatic juice or the cerebrospinal fluid. About 50% of the penicillin passed into the urine, whatever the route of administration. In the rabbit, the substance could rarely be detected in the blood but a good concentration was present in the bile. After intravenous injection 20% to 50% was excreted in the urine, but less than 20% after intestinal administration.

In man, penicillin could be detected in the blood up to 3 hours after intravenous injection or administration by duodenal tube, and was excreted in the urine for 6 hours or more. At least 50% passed into the urine, from which it could be extracted to be used again. Material containing the pyrogenic impurity was freed of the pyrogen by its passage through the body.

The fate of the penicillin not excreted in the urine was not ascertained. There was no appreciable destruction when penicillin was incubated with sterile tissue from a number of organs.

Clinical Therapeutic Trials

Clinical trials were begun on the basis of the properties of penicillin established in the laboratory. Its non-toxicity in concentrations far above those which would inhibit bacteria had been confirmed. It was rapidly eliminated by the kidneys, and frequent or continuous administration was therefore necessary to maintain an anti-bacterial concentration continuously in the body. It was known to be absorbed from the intestine, but as it was destroyed by acid it could be given by mouth only if the stomach were alkalised or the penicillin were enclosed in enteric (acid-resisting) capsules. Faeces destroyed penicillin, probably by bacterial action, so rectal administration was not practicable. It was absorbed from the subcutaneous tissues, but the local effect of injecting concentrated solutions in man was not known.

For these reasons the first human subjects were treated by giving the penicillin intravenously in a "continuous drip" infusion of saline. The dose was injected 2- or 3-hourly into the tubing conveying the saline to the vein or (Case 5) dissolved in the saline and given continuously. Five patients were treated by this method. The first (Case 1) was a febrile and severely emaciated man of 43 with a mixed staphylococcal and streptococcal pyæmia. He was treated for 5 days, after which penicillin supplies were exhausted, but during that time pus formation strikingly diminished and in some sites it ceased altogether and healing started. Appetite and general condition improved and the temperature fell. After 3 days more the patient was afebrile. Equally good results were obtained in a streptococcal wound infection (Case 2) and an acute staphylococcal osteomyelitis with septicæmia (Case 5). A large carbuncle resolved without discharging and without scar formation (Case 3). A boy of 4½ (Case 4), with cavernous sinus thrombosis and lung abscesses due to *Staph. aureus*, became strikingly better during 9 days' treatment with penicillin, the cerebrospinal fluid becoming sterile after 6 days. He was afebrile and appeared on the road to recovery 4 days after the end of treatment when a cerebral vascular accident occurred, due to rupture of a mycotic aneurysm. At *post-mortem* the cavernous sinus region was occupied by granulation tissue, and in the lung, also, healing was in progress. All that remained of the infection was small groups of cocci in microscopic areas of necrosis at the centre of the granulation tissue.

In an infant of 6 months (Case 6) with a persistent urinary infection due to *Staph. aureus*, penicillin was given by mouth with sodium bicarbonate (to neutralise the acid gastric

juice) for 7 days. Though no penicillin could be detected in the blood, the urine became strongly bacteriostatic and the infection disappeared. Three patients with acute conjunctivitis and one with staphylococcal keratitis (Cases 7, 8, 9, 10) were treated by local applications of penicillin. The symptoms were rapidly and strikingly relieved and a quick recovery took place.

During the treatment of these patients there were no toxic symptoms (except for rigors in two cases due to the pyrogenic impurity, which had not been removed). The total leucocyte count usually fell, lymphocytes and polymorphs being equally affected, but the fall ran parallel with the resolution of the infection. The blood urea was slightly above normal in 2 cases, but without any abnormality in the urine.

These results suggested very strongly that penicillin, properly used, would overcome staphylococcal and streptococcal infections in man, though the authors ended by emphasizing that much further investigation would be needed, for which larger supplies of penicillin are essential.

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¹ [see BMB 206] ² [see BMB 203] ³ [see BMB 213]

Further Chemotherapeutic, Bacteriological, and other Investigations

This section includes a wide variety of papers on the biological properties of penicillin and its chemotherapeutic action in experimental infections. Chemical investigations and reports of therapeutic trials in man are described in later sections.

213

SOME BIOLOGICAL PROPERTIES OF HIGHLY PURIFIED PENICILLIN

by H. W. Florey & M. A. Jennings, *British Journal of Experimental Pathology*, 23, 120-123, June 1942

The preparations of penicillin used by Abraham *et al.* (1941) contained 40 to 50 units per mg. [about 4-5 % of pure penicillin]. As soon as preparations containing 250 to 500 units per mg. [25-50 % of pure penicillin] were available, the principal biological tests were repeated on the more active material.

i. *Antibacterial activity.* Growth of the staphylococcus was completely inhibited by a dilution between 1 : 24,000,000 and 1 : 30,000,000 and partially inhibited up to 1 : 160,000,000. The activity towards other organisms was proportionately increased.

ii. *Toxicity to mice.* Mice given 20 mg. intravenously showed no reaction. As 20 mg. of the less pure preparations had caused sickness it was evident that toxicity was diminished with the removal of impurities.

iii. *Toxicity to leucocytes.* Leucocytes survived and moved about sluggishly for an hour in a 1 % solution in spite of its hypertonicity.

The calcium salt. In all previous experiments the sodium salt of penicillin had been used. The calcium salt, unlike the sodium salt, was not hygroscopic and was therefore easier to handle. Ten mg. intravenously, however, produced symptoms in a mouse, and 20 mg. subcutaneously produced immediate distress and subsequent sloughing at the site of injection. Though a 1 % solution caused no reaction in a rabbit's ear it was thought that the calcium salt was unsuitable for therapeutic use. [The preparation of calcium salt tested contained 5 % of penicillin. Calcium salt preparations are in practice found satisfactory for local application if suitably diluted.]

Assay of penicillin. The authors preferred the plate and cylinder method for routine work, keeping the dilution method for occasionally checking the strength of standard

or other preparations. The former method was much quicker and did not require a sterile solution.

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- ¹ Abraham, E. P., Chain, E., Fletcher, C. M., Florey, H. W., Gardner, A. D., Heatley, N. G., & Jennings, M. A. (1941) *Lancet*, 2, 177

¹ [see BMB 212]

214

IN VITRO TESTS OF PENICILLIN POTENCY

by A. Fleming, *Lancet*, 1, 732-733, 20/6/42

In this paper the author surveys the methods available for testing the antibacterial activity of penicillin. The newer antiseptics, of which the sulphonamides and penicillin are the chief examples, differ from the older in two ways: (i) they prevent bacterial growth (bacteriostatic action) instead of killing the bacteria (bactericidal action), and (ii) they act more strongly on some species of bacteria than on others (selective action), instead of acting equally on all species.

With their discovery it became necessary to devise tests which would measure bacteriostatic activity and which did not depend on showing that bacteria had been killed.

Tests with the growing mould. The mould is streaked on one side of a culture plate and grown at a suitable temperature (about 20° C. for *Penicillium notatum*). When the growth is well developed, the bacteria to be tested are streaked across the plate at right angles to the mould. Several species of bacteria can be tested on one plate. If the medium used for the mould is unsuitable for the bacteria it can be covered by a thin layer of another medium before the bacteria are planted, as the penicillin diffuses readily from the old into the new layer of agar.

(a) Qualitative

Tests with Fluid Solutions

i. *The gutter method.* This was described in a previous paper (Fleming, 1929).

ii. *Agar cup method.* A culture plate is inoculated with staphylococcus or some other suitable bacterium. Circular discs are cut out of the agar by a cork borer, and the bottom of the "cup" so formed is sealed with 2 drops of melted agar. The solution to be tested is placed in the cup, whence the active substance diffuses into the surrounding agar. The broth from a satisfactory culture of *Penicillium notatum* inhibits growth for about 15 mm. from the edge of the cup. Graduated dilutions of penicillin produce zones whose width is directly proportional to the concentration of the penicillin. This method, compared with the cylinder method of Abraham *et al.* (1941), requires no special apparatus and is not affected by the presence of erythrocytes which, in the cylinder test, lie on the surface of the agar and prevent diffusion of the active substance.

These two methods are of value as qualitative tests, the former to test a number of bacterial species on one plate, the latter to test a number of samples against one species. The applicability of the test obviously depends on the diffusibility of the active substance in agar; the author suggests that such diffusion may be related to diffusibility in the body and therefore to therapeutic activity.

(b) Quantitative

The titration method. A flask of broth is inoculated with the test organism, and used for making serial dilutions of the penicillin. A volume of 0.5 or 1.0 cm.³ per tube is as satisfactory as a larger volume. The sensitivity of an organism or the activity of a penicillin solution can be accurately measured by this method.

To standardize the test for titrating penicillin it is advisable for all workers to use the same strain of staphylococcus and a uniform inoculum and culture medium. The medium suggested consists of peptone (Evans) 1g.; NaCl 0.5 g.; glucose 1 g.; Andrade's indicator 1 cm.³; water to 100 cm.³. The result is read at 24 hours, and the end-point is shown by a change of the indicator to red.

(c) Tests in the Presence of Blood

Up to 25 cm.³ of blood can be incorporated in an agar plate for the gutter or cup test, or the titration method can be used for any organisms which will grow in blood.

The slide-cell technique is also available and has the advantage that the bacteria which are not inhibited form colonies which can be counted.

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- ¹ [see BMB 212] ² [see BMB 203]

215 ZINC PEROXIDE, PROFLAVINE AND PENICILLIN IN EXPERIMENTAL *CL. WELCHII* INFECTIONS

by J. McIntosh & F. R. Selbie, *Lancet*, 2, 750-752, 26/12/42

The authors, Professor of Pathology and Assistant Pathologist at the Bland Sutton Institute of Pathology of the Middlesex Hospital, London, designed their experiments to show the effect of a single dose of penicillin given locally at the site of an anaerobic infection.

Cl. welchii was grown anaerobically for 18 hours in 4% Difco proteose-peptone in distilled water. An injection containing 2 or 4 × 10⁹ washed bacteria in 0.1 cm.³ with 0.1 cm.³ of 5% calcium chloride was given into the right thigh of each mouse. This was equivalent to at least 100 lethal doses. The infection became generalised in the blood stream within 3 or 4 hours. A dose of 34 Oxford units of penicillin in 0.2 cm.³ was given at the same site. Survival was recorded up to 3 days.

Results. All control mice died within 24 hours. In 3 different experiments, a total of 42 mice treated with penicillin at the time of infection all survived. Five out of 6 mice treated at 2 hours survived, but there were no survivals after treatment at 3 or 6 hours, though life was prolonged.

216 CHEMOTHERAPEUTIC DRUGS IN ANAEROBIC INFECTIONS OF WOUNDS

by J. McIntosh & F. R. Selbie, *Lancet*, 1, 793-795, 26/6/43

The margin of safety between the toxic dose and the therapeutic dose was found, in mice, to be greater for penicillin than for sulphonamides or acridines. Penicillin had no undesirable local effect.

Therapeutic tests were done on mice by injecting intramuscularly 100 minimal lethal doses of the organisms suspended in 2.5% CaCl₂ solution. Thirty-four Oxford units of penicillin were given locally into the same site. The interval between injection and treatment was one hour.

Results. Penicillin was greatly superior to sulphathiazole in the treatment of *Cl. welchii* and *Cl. oedematiens* infections, but somewhat less effective than sulphathiazole against *Cl. septicum*. The acridines occupied an intermediate position.

[A more general summary of this paper, with details of the technical methods used, will be published in a future number of BMB.]

217 COMBINED ACTION OF ANTITOXIN AND LOCAL CHEMOTHERAPY ON *CL. WELCHII* INFECTION IN MICE

by J. McIntosh & F. R. Selbie, *Lancet*, 2, 224-225, 21/8/43

The authors compared the effects of giving antitoxin alone and antitoxin with penicillin to mice infected experimentally with 100 lethal doses of *Cl. welchii* in 2.5% calcium chloride.

When 5 units of antitoxin were given, in one or two doses from 3 to 6 hours after infection, eight out of thirty-six mice survived for 3 days or more. When 50 units of penicillin were given with the antitoxin nineteen out of thirty-six survived. Better results were seen when treatment was started 3 hours after infection than when it was started later. Pro-

flavine was considerably less effective than penicillin as an adjunct to antitoxin.

[A more general summary of this paper, with details of the technical methods used, will be published in a future number of BMB.]

218 LOCAL CHEMOTHERAPY IN EXPERIMENTAL LESIONS OF THE EYE PRODUCED BY *STAPHYLOCOCCUS AUREUS*

by J. M. Robson & G. I. Scott, *Lancet*, 1, 100-103, 23/1/43

The authors, a pharmacologist and an ophthalmic surgeon working in the Department of Pharmacology of the University of Edinburgh, studied the effect of penicillin (and other antibacterial substances) in experimental lesions of the eye due to the staphylococcus.

Technique. A strain of *Staphylococcus aureus* which would produce an acute and severe infection of the eye in rabbits was selected. A 24-hour culture was diluted to contain 1,500 bacteria per cm.³ A hypodermic needle with a blunt bevel was inserted into the cornea and the diluted culture was injected until a small blister was raised under the corneal epithelium.

The severity of the infection varied in different rabbits, but in each rabbit the lesions in the two eyes were remarkably similar. Severe conjunctivitis, corneal ulcers and iritis were always produced, and usually a hypopyon. The final condition varied from slight scarring to gross destruction of the eye.

Penicillin was applied to one eye, and saline solution as a control to the other. Treatment was started 1 hour after the infection and was given every hour for 48 hours and thereafter hourly during the day.

Result. Penicillin was applied to one eye in 17 rabbits and, of these eyes, 14 suffered slight or negligible damage. Among the control eyes, the damage was slight in only one and in the rest was classed as moderate or severe. Cultures from the treated eyes were sterile during treatment and for several days after.

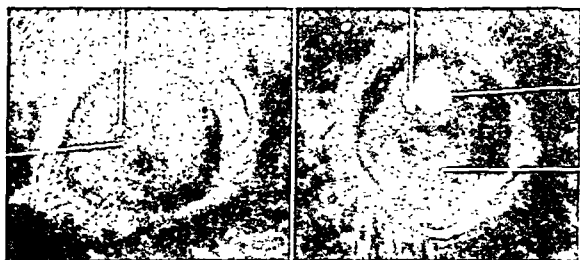


FIG. VI—Condition of eyes of rabbit on 3rd day after inoculation under the corneal epithelium of a staphylococcal culture. In the eye (left side) treated with penicillin, only a faint infiltrate developed, and this later disappeared. In the untreated eye there is considerable corneal ulceration with hypopyon. This photograph is reproduced from the *Lancet*.

When the treatment was started 24 hours after infection it was almost without effect.

[Reference is made above only to those parts of the original paper in which the use of penicillin is described. A more general abstract of the same paper has previously been published (BMB 53).]

219 THE PRODUCTION AND TREATMENT OF EXPERIMENTAL PNEUMOCOCCAL HYPOPYON ULCERS IN THE RABBIT

by J. M. Robson & G. I. Scott, *British Journal of Experimental Pathology*, 24, 50-56, April 1943

Continuing their investigation on the treatment of experimental infections of the eye, the authors produced pneumococcal ulcers in rabbits by injecting a 6 to 15-hour culture of a type 19 pneumococcus into the cornea, so as to raise a small blister under the corneal epithelium. There was some variation in the severity of the resulting lesion, but usually there

was severe ulceration, with iritis and hypopyon. One eye in each rabbit was used as a control. Penicillin was applied to the eye hourly for 36 hours and then hourly by day for about 3 days more.

Result. In 28 rabbits in which treatment was started 1, 6 or 12 hours after infection, all the untreated control lesions were classed as severe, whereas 22 of the treated lesions were classed as slight or very slight. Even when treatment was started at 24 hours there was some effect—8 out of 14 treated lesions were slight, while all the control lesions were severe.

[Reference is made above only to those parts of the original paper in which the use of penicillin is described. A short and more general abstract of the same paper has previously been published (BMB 164).]

220

CHEMOTHERAPEUTIC EXPERIMENTS WITH THE VIRUSES OF INFLUENZA A, LYMPHOGRANULOMA VENEREUM AND VACCINIA

by C. H. Andrewes, H. King, & M. van den Ende, *Journal of Pathology and Bacteriology*, 55, 173–181, April 1943

The authors, who are on the staff of the *National Institute for Medical Research*, London, tested the action of penicillin on mice infected with influenza, vaccinia and lymphogranuloma venereum viruses. The penicillin was injected 3-hourly for 72 hours. It had no therapeutic effect in mice with any of these diseases, in spite of the fact that it suppressed the growth of lymphogranuloma venereum virus in tissue culture.

[This brief abstract refers only to results with penicillin. A fuller summary will appear in a future issue of BMB.]

221

SYNERGISTIC EFFECT OF PARA-AMINOBENZOIC ACID AND SULPHAPYRIDINE ON PENICILLIN

by J. Ungar, *Nature*, 152, 245–246, 28/8/43

The author is a member of the research staff of the *Glaxo Laboratories, Ltd.*, Greenford, Middlesex. He found that in a medium containing 0.1 % hydrolyzed casein the addition of *p*-aminobenzoic acid (1:1,000–1:10,000) raised the figure at which a penicillin solution inhibited *B. subtilis* from 1:100 to 1:6,000 and *Staph. aureus* from 1:40,000 to 1:75,000–1:100,000. A similar effect was seen in glucose broth with *B. subtilis*. There was no effect with *Strept. haemolyticus*.

Sulphapyridine in concentrations too low to inhibit growth (1:2,000–1:50,000) had a similar effect, raising the titre for *Staph. aureus* in digest broth from 1:30,000 to 1:70,000. A similar effect was shown in glucose broth against the staphylococcus and streptococcus. No further rise in titre occurred when *p*-aminobenzoic acid was added as well as sulphapyridine.

Groups of six mice were injected with staphylococci and streptococci and treated for 4 days with small doses of (i) sulphapyridine, (ii) penicillin, (iii) sulphapyridine + penicillin. With the streptococcus 1 mouse in each of groups (i) and (ii) was alive at 7 days, and 4 in group (iii). With the staphylococcus a similar prolongation of life was shown, though the sulphapyridine alone was entirely without effect. Control mice were all dead on the first day. [The groups of mice in this therapeutic trial are too small for the experiment to be considered entirely conclusive.]

222

INHIBITION OF UREASE BY PENICILLIN

by J. C. Turner, F. K. Heath & B. Magasanik, *Nature*, 152, 326, 18/9/43

The authors, who are members of the U.S. Army in Great Britain, reported that highly purified penicillin preparations, with an activity of up to 850 Oxford units per mg., inhibited the action of urease. From results with preparations of different activities it was thought probable that the inhibition was a function of penicillin itself and largely independent of the impurities present.

It was suggested that the elevation of blood urea, found by Florey & Florey (1943) to have occurred in some patients

treated with penicillin, might be attributable in part to *in vivo* inhibition of urease.

[This suggestion should be accepted with reserve, as it is unlikely that concentrations in the body ever approach those used in these *in vitro* tests.]

REFERENCE

¹ Florey, M. E., & Florey, H. W. (1943) *Lancet*, 1, 387

¹ [see BMB 233]

223

THE PRODUCTION OF PENICILLIN

by S. W. Challinor & J. MacNaughtan, *Journal of Pathology and Bacteriology*, 55, 441–446, October 1943

The authors, who are working in the Bacteriology Department and the *Wilkie Surgical Research Laboratory* in the University of Edinburgh, emphasize the difficulty of producing large amounts even of crude penicillin. The mould takes several days to reach maximum production and the yield of penicillin is small. Further, since a shallow layer of culture medium is necessary, large amounts of space are needed for incubation. For these reasons they turned their attention to finding substances which, added to the basic medium, would increase the yield.

The basic medium was the modified Czapek-Dox used by Abraham *et al.* (1941), with 10 % yeast extract. On the assumption that the mould at the height of its activity might produce growth-promoting substances, matured medium (e.g. on the 11th day) was added to fresh medium. This accelerated the production of penicillin but reduced its stability, probably because of the acids formed. A better result was obtained by adding buffers or CaCO₃ to the medium to maintain the pH at about 7. Using a medium of the following composition :

NaNO ₃ . . .	3.0 g.	Na ₂ HPO ₄ .12H ₂ O	33.5 g.
KCl . . .	0.5 g.	Glucose (A.R.)	40.0 g.
MgSO ₄ .7H ₂ O	0.5 g.	Yeast extract	100 ml.
FeSO ₄ .7H ₂ O	0.01 g.	Distilled water	to 1000 ml.
KH ₂ PO ₄ . . .	6.5 g.		

yields in individual cultures were increased 6–8 times, e.g. from 1 to 6 Oxford units per cm.³ By adding 5 cm.³ of a 10 % aqueous suspension of CaCO₃ to 200 cm.³ of basic medium, an increase was also obtained.

The authors observed that the yield varied according to the strain of *Penicillium notatum* employed. Higher yields were reported by workers using other strains. [And are also obtainable on other media, whose formulæ are as yet unpublished.]

REFERENCE

¹ Abraham, E. P., Chain, E., Fletcher, C. M., Gardner, A. D., Heatley, N. G., Jennings, M. A., & Florey, H. W. (1941) *Lancet*, 2, 177

¹ [see BMB 212]

224

A NEW RAPID METHOD FOR PENICILLIN ASSAY

by U. Wilson, *Nature*, 152, 475–476, 23/10/43

The present assay methods for penicillin, all of which depend on bacterial inhibition, usually entail overnight incubation. In this communication the author, who is on the staff of the *Wellcome Physiological Research Laboratories*, describes a test which can be read after 3–3½ hours. Aseptic technique is not necessary.

The penicillin solution to be tested was initially diluted so as to contain about 1 unit per cm.³ and then serially diluted with nutrient broth. To tubes containing 1 cm.³ of these broth dilutions were added 0.2 cm.³ of a suspension of 500–700 × 10⁶ organisms of a group A β-haemolytic streptococcus and 0.8 cm.³ of a 5 % suspension of sheep erythrocytes. After mixing, the tubes were incubated in a water-bath at 37° C. for 3–3½ hours. They were then centrifuged and examined for haemolysis, absence of haemolysis indicating a bacteriostatic concentration of penicillin. The streptococcus was grown on plain agar and washed off with broth before use, to avoid the inclusion of preformed haemolysin.

INHIBITION OF PENICILLIN IN ROUTINE CULTURE MEDIA

by G. J. Harper, *Lancet*, 2, 569-571, 6/11/43

In making bacteriological investigations into the results of treatment with antiseptics, it is a serious difficulty that traces of antiseptic may be carried over into the cultures and prevent the growth of bacteria which are present. The author of this paper, who is senior technical assistant in the *Medical Research Council Unit* at the Birmingham Accident Hospital, describes a method for removing penicillin when making such cultures. For this purpose he utilised the discovery of Abraham & Chain (1940) that certain bacteria contain an enzyme, penicillinase, which destroys penicillin.

Strains of *Bact. coli*, *Bact. aerogenes*, *Bact. typhosum*, *Bact. typhi-murium*, *Bact. flexneri*, *Ps. pyocyanea*, *Proteus vulgaris*, and an air micrococcus, all inactivated penicillin to a greater or less degree, but the most powerful inactivator was the paracolon bacillus, of which 7 strains isolated from penicillin-treated wounds were all found to destroy penicillin. Living cultures, culture filtrates and dried preparations of this bacillus all appeared to be active. For bacteriological use, the 24-hour growth on a solid medium was suspended in the minimum amount of distilled water and precipitated with acetone. After standing an hour the precipitate was treated for 1-2 hours with fresh acetone and then with two changes of ether. After centrifuging, the precipitate was dried quickly *in vacuo* and stored in sterile tubes. The preparation, dry or suspended in water, remained active for at least several weeks.

One mg. of the dry preparation incorporated in a culture tube or plate was shown to inactivate 200 Oxford units of penicillin, an amount greater than that likely to be accidentally encountered in routine work. The paper contains tables showing the success of this method in obtaining a growth of penicillin-sensitive organisms from swabs of penicillin-treated wounds, which on ordinary media appeared to be sterile.

REFERENCE

¹ Abraham, E. P., & Chain, E. (1940) *Nature*, 146, 837

¹ [see *BMB* 210]

226

THE ACTION OF CHEMOTHERAPEUTIC DRUGS (INCLUDING PROFLAVINE) AND EXCIPIENTS ON HEALTHY TISSUE

by F. R. Selbie & J. McIntosh, *Journal of Pathology and Bacteriology*, 55, 477-481, October 1943

In the course of testing the effect of antiseptics administered locally the authors injected intramuscularly in mice 5 mg. of an impure preparation of the calcium salt of penicillin [concentration of penicillin not stated], dissolved in a small amount of water. The mice were killed at 3 days. No details of the findings are given but it is stated that muscle necrosis was slight—less than that caused by any other antiseptic tested except the sulphonamides, which produced a similar degree of necrosis.

Purification and Investigation of Chemical Properties

Communications on this subject are few, and although the chemistry of penicillin is receiving urgent attention on both sides of the Atlantic, full results are not yet available for publication.

227

PURIFICATION AND SOME PHYSICAL AND CHEMICAL PROPERTIES OF PENICILLIN

by E. P. Abraham & E. Chain, *British Journal of Experimental Pathology*, 23, 103-115, June 1942

In this paper from the *Sir William Dunn School of Pathology*, Oxford, the authors report in full their chemical investigations up to the time of publication. They give a method for

obtaining a penicillin preparation with an activity of 500 Oxford units per mg., and describe some of its physical and chemical properties. Growth of the mould and assays of antibacterial activity were carried out as previously described (Abraham *et al.*, 1941).

Owing to the instability of penicillin, methods of purification were restricted to those depending on distribution between solvents, adsorption, and reduction. Most of the operations were carried out at temperatures of less than 7° C.

The acid properties of penicillin made it possible to extract the substance with certain organic solvents at pH 2 and to re-extract it into water, as a salt, at pH 6. Penicillin was extracted from the culture fluid by an equal volume of amyl acetate and then converted to the barium salt (20 units/mg.) in one-fifth of the volume of water. Inactive pigment was removed from the solution by treatment with 5 % of charcoal. The penicillin was then transferred to ether and the ethereal solution was passed through a column of Brockmann alumina. The chromatogram showed the presence of at least five different pigments, the penicillin being associated with a light yellow layer near the top of the column. The material was eluted from this fraction by phosphate buffer at pH 7, extracted by ether and converted to the barium salt (70-100 units per mg.). A second chromatogram gave material of 100-150 units per mg. On reduction of this material with aluminium amalgam, keeping the aqueous solution neutral, most of the remaining pigment was adsorbed by the alumina formed. The supernatant contained 80 % of the original activity and yielded, after extraction with amyl alcohol, a barium salt of about 300 units per mg. After three further chromatographic adsorptions from amyl acetate, the final column appeared almost colourless and homogeneous. From this was obtained a barium salt of 450-500 units per mg. Elementary analysis gave the following figures: C 44.3; H 4.8; N 4.2; Ba 22.0.

The barium salt was most stable in aqueous solution between pH 5.5 and 7.5; though under these conditions it was rapidly inactivated by heating to 100° C. It was quickly inactivated by dilute acid and alkali at room temperature, but at 0° C. could be kept for one hour at pH 2. The free acid was hygroscopic and lost activity readily, but its solution in ether or amyl acetate was stable for some days.

Penicillin was inactivated by: (i) heavy metal cations, such as copper and mercury, (ii) primary alcohols, (iii) ammonia and amines, (iv) hydrazine, hydroxylamine and bisulphite, (v) oxidising agents such as permanganate or hydrogen peroxide.

Inactivation by acid, alkali and by boiling at any pH was shown to be accompanied by definite chemical changes. Active penicillin showed no buffering power between pH 6 and pH 10, but inactivation with acid resulted in the formation of a new titratable group with a pK of approximately 7.6. At the same time a substance precipitated by base precipitants was formed. Dilute alkali produced a group with a pK of approximately 5.0. It was not possible to produce both these groups. Treatment with alkali after acid, or *vice versa*, resulted in no further change. This suggested that the same part of the molecule was involved in both acid and alkaline inactivation. Inactivation by boiling at any pH was shown to be accompanied by the loss of a molecule of carbon dioxide.

REFERENCE

¹ Abraham, E. P., Chain, E., Fletcher, C. M., Gardner, A. D., Heatley, N.G., Jennings, M. A., & Florey, H. W. (1941) *Lancet*, 2, 177

¹ [see *BMB* 212]

228

THE SPECTROGRAPHIC EXAMINATION OF PENICILLIN PREPARATIONS

by E. R. Holiday, *British Journal of Experimental Pathology*, 23, 115-119, June 1942

The author, who is a member of the Medical Unit of the *London Hospital*, examined the ultra-violet absorption spectra of penicillin preparations at various stages of purification (Abraham & Chain, 1942).

With increase in the purity of the penicillin there was a fall in the intensity of absorption. Before the stage of reduction with aluminium amalgam, preparations showed high specific extinction coefficients with two distinct maxima at 278–283 $m\mu$ and 375–388 $m\mu$. After the reduction they showed low extinction coefficients with one maximum at shorter wavelengths (246–254 $m\mu$) and a pronounced long wave inflexion (300 $m\mu$). The values for material with an activity of 480 units per mg. were $E_{0.1\%}^{247m\mu} = 8.5$ and $E_{0.1\%}^{300m\mu} = 2.3$.

The absorption curves showed that most of the material in crude penicillin preparations was chemically changed during the reduction, but it was not possible to state whether the portion changed included penicillin itself.

The molecular extinction coefficient of the purest material was thought to be too low to allow the presence of substituted aromatic rings, but a polysubstituted hydroaromatic ring structure was considered possible.

REFERENCE

¹ Abraham, E. P., & Chain, E. (1942) *Brit. J. exp. Path.* **23**, 103

¹ [see *BMB* 227]

229

PURIFICATION AND CHEMISTRY OF PENICILLIN

by J. R. Catch, A. H. Cook & I. M. Heilbron, *Nature*, **150**, 633–634, 28/11/42

Professor Heilbron and his co-workers at the *Imperial College of Science*, London, describe the purification of penicillin by a modified form of chromatography. Penicillin dissolved in an organic solvent, such as ether or amyl acetate, was passed through a column consisting of a 2.5% precipitate of an alkaline earth carbonate on silica-gel. The constituents of the crude penicillin were thought to be separated primarily according to the strengths of the component acids.

By this process the authors obtained a penicillin strontium salt having an activity stated to be about 500 Oxford units per mg. The material gave analytical figures corresponding with the formula $C_{24}H_{34}O_{11}NSr$. [It is clear from other work that this is not the correct formula for penicillin.]

The substance was degraded by treatment with dilute acid, alkali, or moist organic bases such as aniline. The products isolated were: (a) a colourless water-soluble acid, (b) varying quantities of a yellow almost insoluble pigment, (c) acetaldehyde. The water-soluble acid afforded ether-soluble and ether-insoluble acids on further hydrolysis. The latter gave a positive ninhydrin reaction and was considered to be formed by the splitting of a peptide bond.

230

PENICILLAMINE, A CHARACTERISTIC DEGRADATION PRODUCT OF PENICILLIN

by E. P. Abraham, E. Chain, W. Baker & R. Robinson, *Nature*, **151**, 107, 23/1/43

These chemical workers in the *Sir William Dunn School of Pathology* and the *Dyson Perrins Laboratory*, Oxford, collaborating to elucidate the constitution of penicillin, report that solutions of penicillin hydrolysed by N/10 sulphuric acid at 100° C. give a strong ninhydrin reaction. The colour intensities given by numerous preparations run parallel to their antibacterial activities. Hydrolysates of the purest preparations (650 and 1,000 Oxford units/mg.) contained about 59% of their total nitrogen in the form of amino nitrogen. The authors believe the substance responsible for these results to be a fundamental part of the penicillin molecule, and have named it penicillamine.

Penicillamine was precipitated from solution by mercuric chloride. After decomposing the precipitate, crystalline penicillamine hydrochloride was obtained in 30%–40% yield.

Penicillamine showed no measurable rotation in aqueous solution. It had three titratable groups with pK values of 2.0, 7.9 and 10.5. The nitrogen was present as an amino group. Penicillamine gave a deep blue colouration with ferric chloride. It was oxidised by iodine, the reaction being reversible. On heating with *p*-nitro-phenylhydrazine in N hydrochloric acid, glyoxal *p*-nitrophenylosazone was produced in 20% yield.

231

PENILIC ACID, AN OPTICALLY ACTIVE ACID FROM PENICILLIN

by W. M. Duffin & S. Smith, *Nature*, **151**, 251, 27/2/43

The authors, working at the *Wellcome Physiological Research Laboratories*, found that when highly active penicillin preparations were kept in aqueous solution at pH 2 there occurred a rise in rotation. Only part of the material could then be extracted by ether, and there was left in the colourless aqueous phase a substance which they named penillic acid. This could be extracted from the aqueous solution by butyl alcohol, from which it could be separated in crystalline condition. The yield was directly proportional to the biological activity of the penicillin used. With the best material it amounted to 20% of the barium penicillin.

Penillic acid decomposed at 175° C. with evolution of gas. In aqueous solution it had a rotation of +600 for the mercury green line. It gave a bluish-purple colour with ninhydrin. It was precipitated by mercuric chloride and phosphotungstic acid, and formed a sparingly soluble silver salt. It did not show the blue colouration with ferric chloride found by Abraham *et al.* (1943) to be given by penicillamine.

REFERENCE

¹ Abraham, E. P., Chain, E., Baker, W. & Robinson, R. (1943) *Nature*, **151**, 107

¹ [see *BMB* 230]

Further Clinical Trials

The first clinical trials of penicillin were part of a comprehensive investigation which is reported under another heading. The clinical reports described here, although limited by the relative scarcity of penicillin, provide conclusive confirmation of its therapeutic value. The first of the reports below is not comparable in scope with the others, but it is an interesting example of an early clinical application of penicillin.

232

ANTISEPTIC SNUFFS

by M. E. Delafield, E. Straker & W. W. C. Topley, *British Medical Journal*, **1**, 145–150, 1/2/41

This paper, by three members of the *Emergency Public Health Laboratory Service*, described the technique used and the results obtained in some preliminary experiments on the control of the bacterial flora of the nose and nasopharynx by means of antiseptics applied locally in the form of a snuff.

The subjects were examined on 3 successive days each week. Two nasal, one pharyngeal and two tonsillar swabs were taken. Each swab was immediately emulsified in 2 cm.³ of nutrient broth, the swab being rotated 20 times and then pressed against the side of the bottle. After this had been repeated 3 times, 0.6 cm.³ of the broth was pipetted into the middle of a sterile Petri dish, and then absorbed on to a sterile 7-cm. filter paper. The paper was transferred to the surface of a blood-agar plate. After contact had been made the paper was removed and the plate was incubated at 37° C. Examinations were made at 24 and 48 hours. After 48 hours the plates were photographed against a dark background with oblique back-lighting. The number of colonies was counted in the prints. The method gave better quantitative results than other methods tried, but the normal variation was found to be large. Growth was usually heaviest from the tonsils and least from the nasal cavities.

Of the three antiseptics used, sulphathiazole (10% in lycopodium powder or in magnesium carbonate as a diluent) was given the most extensive trial. Proflavine (5%) was soon found to be less effective and was also aesthetically objectionable. Penicillin was then so scarce that only 4 cases could be treated with it.

The penicillin snuff contained 1 part by weight of penicillin, 5 parts of menthol and 94 parts of lycopodium. [The penicillin used was a crude preparation of the sodium salt containing about 10 Oxford units per milligram. With six applications a day the daily dose of penicillin was about 25 to 35 units.]

Results. The 4 cases treated with penicillin were all relatively heavy nasal carriers of staphylococci. The numbers of staphylococci were greatly decreased during treatment. In

3 cases the period of treatment was short (7-10 days), and staphylococci returned after the penicillin was discontinued. The authors point out that, though traces of antiseptic carried over on the swabs could not always be excluded as a cause of the reduced bacterial count, in one case staphylococci were almost abolished for 8 days after a short course of penicillin.

Nineteen cases were treated with sulphathiazole snuff with promising results, but the number of cases was too small to permit a critical evaluation of the method of treatment. The authors conclude that (i) further work on proflavine is not worth while, (ii) penicillin would probably prove particularly effective, (iii) sulphathiazole might be tried in larger doses with better results, and (iv) a mixture of penicillin and sulphathiazole might prove useful.

Treatment of carriers by this method would probably need to be prolonged.

233

GENERAL AND LOCAL ADMINISTRATION OF PENICILLIN

by M. E. Florey & H. W. Florey, *Lancet*, 1, 387-397, 27/3/43

Professor Florey and Dr. M. E. Florey report in this paper the first wide investigation of the possibilities of penicillin therapy. Fifteen patients with serious illness were treated by mouth or by intravenous or intramuscular injection and 172 patients were treated by local application.

The principles of clinical use were based on the knowledge already obtained in the laboratory: (i) Because penicillin had been found to be destroyed by boiling, by acids, alkalis and certain heavy metals, by oxidising agents and by enzymes produced by some common air bacteria, it was clear that solutions for clinical use must be freshly made up and protected particularly from changes of pH, from heat and from bacterial contamination. (ii) In concentrations suitable for clinical use, penicillin is bacteriostatic, not bactericidal; a concentration sufficient to suppress bacterial growth must therefore be maintained continuously at the site of infection until the physiological defence mechanisms have effectively acted upon the invading organisms. (iii) It was known that penicillin is excreted rapidly by the kidneys; therefore in systemic administration large and frequent doses were necessary to maintain a bacteriostatic concentration continuously in the body. (iv) No toxic effects had been seen after therapeutic doses in mice or men. Leucocytes survived in high concentrations of penicillin. There was therefore no problem of overdosage. (v) It was known that neither tissue extracts, blood, nor pus interfered with the antibacterial action of penicillin.

Systemic Administration

By mouth. As penicillin would have been destroyed by the acid gastric juice it was necessary to give it in "enteric capsules" (gelatine capsules coated with cellulose acetate phthalate, which is soluble in alkali but not in acid) or by duodenal tube. Preliminary trials on a normal subject showed that the penicillin given by capsule was absorbed, as the blood became bacteriostatic for 2 hours and the urine for 7 hours, but the time at which the capsules dissolved was variable. An attempt was made to treat two patients by capsule and duodenal tube, but there was no marked clinical improvement and it is probable that absorption was irregular and incomplete and the dosage too small.

Parenteral. Of the remaining 13 cases treated by general administration, 5 received penicillin intramuscularly alone, 5 both intravenously and intramuscularly, and 3 received local injections at the site of infection in addition to injections by one or both of the other routes. Sometimes a continuous intravenous saline drip was established and the penicillin was given intravenously by this means. The usual dose for an adult was 10,000 Oxford units 2-hourly, or 15 or 20,000 units 3-hourly, but the size of the dose was never arbitrary. By a modification of the slide-cell technique of Colebrook, Storer & Wright (1923) the power of the patient's plasma to prevent the growth of the infecting organism was tested at various intervals between one injection and the next, and the dose was so regulated as to maintain bacteriostasis continuously in the plasma. The largest total dose was 4.7 million units to a patient who was treated continuously for a month. The usual total dose for an adult was about 1.5 million units. As little as 0.1 million units brought

about the recovery of an infant of 2 months with multiple osteomyelitis.

Of this group of cases 8 had a severe infection with *Staph. aureus*—acute or sub-acute osteomyelitis, pyæmia or septicæmia with, in one case, fulminating cavernous sinus thrombosis—and all were cured, as was also a patient with chronic osteomyelitis in which *Staph. aureus* and *Strept. pyogenes* were combined. A case of meningitis due to a sulphonamide-resistant streptococcus [reported fully by Fleming (1943)] was cured. In a patient infected with a streptothrix and a streptococcus the streptothrix was eliminated. In another case with a similar mixed infection the organisms were not eliminated, but here the dose of penicillin was clearly too small. A case of sub-acute bacterial endocarditis due to *Strept. viridans* improved during treatment but relapsed as soon as treatment was stopped, at the end of a month.

Certain important facts emerged from the study of these cases. Penicillin prevented bacteria multiplying but had no other effect, and the body defences were therefore called on to overcome the residual infection in the usual way; for this reason the temperature fell slowly over 1 to 2 weeks and was not a guide to the success of treatment in the first few days. By contrast, diminution of pain and improvement in spirits and appetite began early and were usually remarkable. Elimination of bacteria ran parallel with recovery. Where bones were involved, radiograms taken during the period of recovery showed a progressive rarefaction which was presumed to be due to the rapid removal of inflammatory products; recalcification took place later without further treatment. In some cases the blood urea rose, but it fell again during or after treatment; the urine did not contain albumen and there was no sign that the rise was due to renal damage. Anæmia improved during treatment without blood transfusion, and there was no evidence of toxic leucopenia. In 5 cases the infecting organism was isolated before and after treatment and tested against penicillin *in vitro*. In 3 cases there was no change in sensitivity; in 2 cases slight resistance had developed to the extent that four times the previous concentration of penicillin was needed to inhibit growth.

Local Administration

The same principles as for general treatment were applied. Penicillin was known to act in the presence of pus, but being very soluble had to be renewed frequently. A good effect could be expected only if the whole infected area could be reached, but free drainage, which would have removed the penicillin, was not desirable. (The calcium salt of penicillin was used in most cases as it was easier to handle than the sodium salt, which was hygroscopic. The calcium salt was not, however, suitable for intravenous or intramuscular injection in strong solution.)

The cases treated fell into 4 groups:

i. *Mastoid infections.* After a Schwartze mastoidectomy the wound was sewn up completely and a fine rubber tube without lateral holes was inserted through the upper end to the base of the cavity. Penicillin solution, 250 to 500 units per cm.³ was injected 6-hourly, exudate being aspirated through the tube before each injection. Penicillin ointment was smeared on the suture line. Treatment was continued for 7 days. Fourteen out of 16 acute or sub-acute and 5 out of 6 chronic cases healed by primary union. Two of the failures came early in the series and could be attributed to technical defects.

ii. *Eye infections.* Eighty-nine eye infections of a wide variety of types were treated by aqueous drops or vaseline ointment containing 600 to 800 units of penicillin per cm.³ or gram. Among the infecting organisms were *Staph. aureus*, *Staph. albus*, pneumococcus and gonococcus. A large proportion of the cases was cured. Relapse or failure could always be explained by persistence of an insensitive organism, an associated irritative condition, or failure to persevere with treatment.

iii. *Chronic wound sinuses.* Dry penicillin powder was applied to short sinuses. Long sinuses were treated by inserting a catheter as far as possible, injecting penicillin solution (200-500 units/cm.³) and immediately closing the sinus with a rubber bung. The injections were given twice daily for from 10 to 21 days. Sinuses associated with empyema were treated by injecting the solution twice daily and closing the aperture except for an hour before each injection. Nine out of eleven sinuses healed within a month, the remaining

two requiring surgical treatment for a sequestrum and a bronchopleural fistula respectively.

iv. *Various septic conditions.* Among 50 patients with a variety of septic lesions, healing was obtained by similar methods in all but a few, for whom surgical interference was needed to obtain better access or to drain already sterilised abscesses.

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¹ Fleming, A. (1943) *Lancet*, 2, 434

¹ [see BMB 236]

234

PENICILLIN AND PROPAMIDINE IN BURNS : Elimination of Hæmolytic Streptococci and Staphylococci

by A. M. Clark, L. Colebrook, T. Gibson, M. L. Thomson & A. Foster, *Lancet*, 1, 605-609, 15/5/43

This paper is by members of the *Medical Research Council Burns Unit* at the *Royal Infirmary*, Glasgow, who report the results of local penicillin therapy in infected burns. The control of sepsis due to hæmolytic streptococci and staphylococci was desirable not only for treatment but also to eliminate the dangers of cross-infection.

Method. Penicillin was incorporated in a cream consisting of lanette wax SX 50 g., castor oil 120 cm.³, water 275 cm.³ Sufficient of the calcium salt of penicillin, dissolved in a small amount of water, was added to the cream to give a final concentration of penicillin of 120 units/gram. It was found that the bacteriostatic activity of the cream was retained at room temperature for about 2 weeks. The cream was thickly spread over the burns and renewed 4 times at 48-hour intervals.

Results. No toxic effects were observed and the dressings were painless. Healing was rapid except when delayed by large sloughs or gross skin loss. Forty-one out of 54 wounds were freed from hæmolytic streptococci within 5 days. In the remaining cases healing occurred less rapidly on account of adverse circumstances (*e.g.* interference with the dressings). Staphylococci also disappeared, though more slowly. The authors suggest that a greater concentration of penicillin would have been an advantage.

*Propamide*¹ (an 0.1 % cream) was used in the same way, but it was less effective and there was, further, a danger of toxic absorption. Neither material had any effect on coliform bacilli, *B. proteus*, or *Ps. pyocyanea*, in cases in which these organisms were present.

¹ [see BMB 58 for an account of this new drug.]

235

LOCAL THERAPY OF WAR WOUNDS : 1. With Penicillin

by R. J. V. Pulvertaft, *Lancet*, 2, 341-346, 18/9/43

The author, who is the Officer Commanding the Central Pathological Laboratory of the Middle East Forces, opens this paper by describing a simple suction apparatus which he considers almost essential for removing pus from septic wounds before applying antiseptic dressings. A glass nozzle connected with a suction bottle emptied by gravity was applied to the wound, while simultaneously saline solution (the author suggests that 0.1 % electrolytic hypochlorite solution might have been better) was run over the wound by gravity through another nozzle connected to a glass reservoir. By this apparatus pockets could be thoroughly cleaned, and smell and soiled dressings could be greatly reduced.

Penicillin, either the calcium or sodium salt, was applied as a dry powder, a spray, or a wet dressing under paraffin gauze. Occasionally the powder caused transient pain. Detailed reports are given of 15 treated cases, all of which had war wounds with severe sepsis. The results were uniformly good. Within one or two days of beginning penicillin applications, the appearance of the wounds improved and discharge stopped. Gram-positive bacteria largely disappeared, any that remained becoming intracellular. In a few days healthy granulations and epithelial growth were seen, at which stage cultures were often sterile. Sometimes gram-negative bacilli increased in numbers, but they did not produce signs

of inflammation. One patient with gas gangrene, who was delirious from toxæmia, recovered without any other treatment. In another case a brain abscess was successfully treated by penicillin powder (calcium salt) applied at operation and penicillin solution injected through a catheter for the next 3 days.

In some *in vitro* experiments the author showed that the activity of penicillin was not reduced by *p*-aminobenzoic acid, by filtrates of *Staph. aureus* cultures, or by the filtrates of a culture in which *Ps. pyocyanea* had grown in the presence of penicillin. *S. typhi*, grown in the presence of penicillin, produced filamentous forms, showing that division was arrested; such forms could not be subcultured and would presumably be readily ingested by phagocytes.

236

STREPTOCOCCAL MENINGITIS TREATED WITH PENICILLIN : Measurement of Bacteriostatic Power of Blood and Cerebrospinal Fluid

by A. Fleming, *Lancet*, 2, 434-438, 9/10/43

This paper reports fully a case of which some notes were given by Florey & Florey (1943). Penicillin was administered intrathecally for the first time in man, in conjunction with intramuscular injections. The detailed observations made by the author established the value of intrathecal injection and led to the treatment of subsequent cases of meningitis by intrathecal injection alone.

The patient was a man of 52 who had been febrile for 7 weeks and had had signs of meningitis for 3 weeks. There had been an early response to sulphapyridine, but afterwards sulphathiazole was without effect. About 6 colonies per cm.³ of a non-hæmolytic streptococcus were isolated from the cerebrospinal fluid 6 and 2 days before penicillin treatment was begun, by the use of "sloppy" glucose agar cultures (0.2 % agar), after ordinary culture methods had failed.

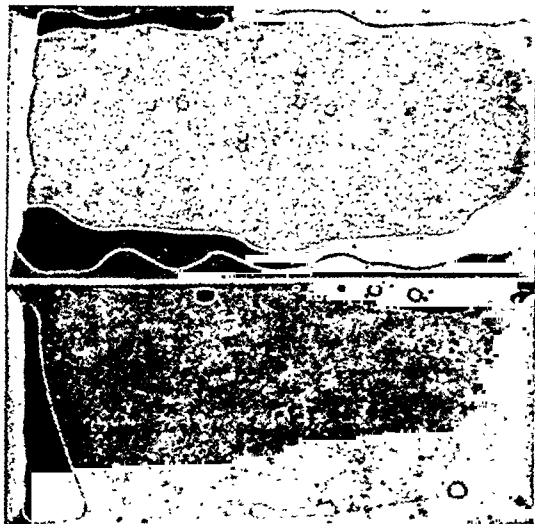


FIG. VII—Testing the bacteriostatic power of a patient's serum by the slide-cell technique. The upper picture shows growth of staphylococci from an inoculum of a 24-hour broth culture (2.5 mm.³ of a 1:80,000 dilution) in a slide-cell, using the patient's serum *before treatment* as the culture fluid. In the lower picture, the patient's serum *after penicillin treatment* has been used, and the absence of staphylococcal colonies indicates that it has acquired strongly bacteriostatic properties. Photograph reproduced from the *Lancet*.

The patient's serum specifically agglutinated this organism, which was shown *in vitro* to be insensitive to sulphathiazole and sensitive to penicillin, though less so than a sensitive strain of *Staph. aureus*.

When penicillin treatment was started the patient appeared to be moribund. Some improvement occurred on 2-hourly intramuscular injections (usually 10,000 Oxford units), and further improvement when intrathecal injections (usually 5,000 units) were given once daily in addition. On one occasion the penicillin was dissolved in the patient's serum for injection, with the object of providing opsonins. Treatment was continued for 14 days, after which the patient's condition was excellent. Recovery was complete.

By *in vitro* tests the author was able to show that during intramuscular therapy the cerebrospinal fluid had only half

the bacteriostatic power of the blood serum, but that intrathecal injections greatly raised its titre. At the best, 24 hours after an intrathecal injection, the cerebrospinal fluid inhibited *Staph. aureus* at 1:160 and the patient's streptococcus at 1:40, compared with 1:2 and 1:1 for the serum 2 hours after an intramuscular injection. The cerebrospinal fluid was coloured yellow by the penicillin.

The bacteriostatic power of the serum was tested by micro-methods based on the fact that staphylococci and streptococci will grow as well-defined colonies in human serum, either whole or diluted with saline up to 1:100 or more.

i. *Slide-cell cultures.* On a waxed slide were placed 50 mm.³ volumes of the diluting fluid (normal serum diluted, e.g. 1:10 with saline); 2:3 or 1:2 serial dilutions of the serum to be tested were made on the slide, 2.5 mm.³ of a diluted culture of staphylococcus or streptococcus was added, and the resulting fluids were run into slide-cells and sealed and incubated.

The bacterial cultures used in this test were so diluted as to produce between 15 and 50 colonies from the 2.5 mm.³ used.

ii. *Capillary tube cultures.* Twenty-five mm.³ of the patient's serum (whole or diluted) mixed with 2.5 mm.³ of culture diluted as above, was run into a capillary tube, which was then sealed and incubated.

iii. *Use of hæmolysis as indicator.* Defibrinated human blood, freed of leucocytes, was added in equal volume to serial dilutions of the patient's serum in saline (25 mm.³ volumes). A loopful of culture of a hæmolytic streptococcus was added to each preparation and the fluids were run into slide-cells (when testing bacteriostasis due to sulphonamides the culture had to be considerably diluted, but this was not necessary with penicillin). After incubation hæmolysis was easily seen wherever the streptococci grew.

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¹ Florey, M. E., & Florey, H. W. (1943) *Lancet*, 1, 387

¹ [see BMB 233]

237

PENICILLIN IN WAR WOUNDS: A Report from the Mediterranean

[unsigned] *Lancet*, 2, 742

THE TREATMENT OF WAR WOUNDS WITH PENICILLIN

by L. P. Garrod, *British Medical Journal*, 2, 755-756, 11/12/43

These are reviews of "A preliminary report to the War Office and the Medical Research Council on investigations concerning the use of penicillin in war wounds. Carried out under the direction of Professor H. W. Florey and Brigadier Hugh Cairns." This memorandum, published by the War Office in London, has a limited circulation and is not generally available.

Work in England and America had established that among the organisms most sensitive to penicillin were three of those most damaging in war wounds—*Streptococcus pyogenes*, staphylococci and the clostridia. It had further amply established that infections by the pyogenic cocci, however severe, could usually be controlled by penicillin. When penicillin was taken to the Mediterranean theatre of war, therefore, the object was not to establish its effectiveness, but to ascertain the best and most economical methods of use to prevent sepsis in battle casualties. The principles of use were those already established in the laboratory and clinic. As supplies of the drug were extremely limited, attention was always directed to using the smallest amount. In this series, therefore, parenteral injection was reserved for those in whom local application could not be expected to reach all infected areas, although with plentiful supplies many more patients would probably be treated parenterally.

The technique of local application was studied fully. It was not found possible to compare the results with those obtained by current methods of treatment, but it appeared that in the ordinary way large numbers of the more serious war wounds became infected. The effectiveness of the sulphonamides, which were widely used for battle casualties, was still neither established nor disproved.

Chronic sepsis. The first patients treated had septic wounds from 3 weeks to 4 months old, none of which had

responded to sulphonamides. Considerable success was obtained in soft tissue wounds by local application of penicillin; bacteria disappeared and the wounds became clean. Compound fractures were beyond the effective reach of local applications, but some recovered on parenteral administration. In others, the extensive suppuration was maintained by insensitive organisms after those sensitive to penicillin had been eliminated. It was felt that to treat sepsis at this stage was wasteful of penicillin and of man-power, both military and medical, and the next series was treated at the Forward Base Hospital.

Recent soft tissue wounds. Current army practice was to excise the wound at the Casualty Clearing Station and leave it open. At the Forward Base Hospital some of the cleanest wounds were then sutured, but many were allowed to heal by granulation, followed later in some cases by delayed suture or grafting. Nearly all such wounds contained pathogenic organisms, and many became septic. The technique for using penicillin in soft tissue wounds at the Forward Base Hospital was as follows. After conservative excision, the skin in particular being as far as possible preserved, the skin was undercut to mobilise the edges. The wound was closed by deep skin sutures, occasionally with muscle sutures in addition. From 1 to 5 fine rubber tubes were inserted through stab holes or through the incision, reaching to the base of the wound and protruding through the dressings at the free end. Three cm.³ of a 250 unit per cm.³ penicillin solution were injected immediately through a syringe attached to each tube, and thereafter 12-hourly for 4 or 5 days. Many wounds were healed in 10 to 12 days, and by 3 weeks complete healing had taken place in 104 out of 171 cases and incomplete healing (i.e. with a small area of granulation in some part of the wound) in 60 more. Only 7 were classified as failures. Pus due to *Ps. pyocyanea*, *B. proteus* or coliform organisms was often formed, but it caused no inflammatory reaction and did not delay healing unless there was a dead space in which it could accumulate.

Even the largest wounds healed completely when treated in this way. There was general agreement that healing was complete in about half the customary time, and that scar formation and permanent disability were very greatly reduced. It is emphasised that under no circumstances should a wound be sewn up in this way in the forward areas, but only in a hospital where the patient can remain.

In another series of patients penicillin-sulphonamide powder, 5,000 units per gram, was insufflated at the Casualty Clearing Station, and suture with tubes, or powder insufflation, was carried out at the Forward Base Hospital. About half the wounds were sterile when received at the Forward Base Hospital; the final result as regards healing was similar to that of the first group.

Compound fractures. These were too extensive for local treatment, and were treated by parenteral administration after suture of the wounds. About 100,000 units of penicillin were given daily for the first 3 days and 50,000 for 2 days more. On this dosage the less serious fractures did well, but some failures were recorded, particularly in fractured femur. Out of 31 patients, complete skin union occurred in 16, partial union in 10, and failure in 5. It seemed clear that with a larger dose better results might be achieved, and a total of 700,000-1,000,000 units in 5-10 days for femur and tibia, and of 500,000 units for other fractures, was recommended for future use. Preliminary treatment with penicillin powder at the Casualty Clearing Station was an asset in achieving a good result, and it was recommended that penicillin in the forward areas should be reserved for compound fractures.

Gas gangrene. Seven patients were treated parenterally and 4 recovered. In 2 who died the infection had been arrested and death was caused by toxæmia. It was concluded that penicillin should not obscure the necessity for excision of all dead muscle and for giving massive doses of anti-gas-gangrene serum. Its greatest use for gas gangrene would probably be as a prophylactic.

Head wounds. As the results of current methods of treating fresh head wounds were very good, penicillin was reserved for penetrating wounds more than 3 days old. Of 23 wounds from 3 to 12 days old, almost all were infected with gram-positive pyogenic organisms and about half were suppurating. The principle of closure with tubes was employed. Twenty cases healed satisfactorily and three died. In one of these

the infection had been controlled, in another only coliform organisms were present at autopsy, and the third, with an 8-day old brain wound containing pneumococcal abscesses, received too little penicillin.

Other groups of cases. A few cases of spinal cord injury and of burns infected by sulphonamide-resistant streptococci were treated with good results.

Ten cases of gonorrhoea, 9 of them sulphonamide-resistant, were treated with an arbitrary dose of 12 injections in 48 hours, totalling 180,000 units. Immediate cessation of discharge, "like turning off a tap," was invariable. There was no relapse during the time of observation (2 to 4 weeks).

238

INFECTED BURNS AND SURFACE WOUNDS: The Value of Penicillin

by D. C. Bodenham, *Lancet*, 2, 725-728, 11/12/43

The author, who is officer in charge of a *Royal Air Force* Burns Unit, briefly discusses the infective processes liable to complicate burns and the principles of first aid and hospital treatment. Of 150 major burns a large number were infected with streptococci and nearly all with staphylococci. Streptococci on the surface of a burn, unless sulphonamide-resistant, could be reduced in numbers, though rarely abolished, by sulphonamides. Staphylococci were hardly affected by any sulphonamide except sulphathiazole, and in comparison with penicillin the action of this drug was slight.

Pseudomonas pyocyanea and *Bacillus proteus*, which are resistant to sulphonamides and penicillin, were found as secondary invaders of many infected burns. The pus they produced sometimes interfered mechanically with skin grafts, but they did not delay epithelialisation.

Seventy-five burns of a duration of 7 to 180 days were treated with penicillin. All but 6 had previously received sulphonamide treatment. Penicillin eliminated staphylococci and streptococci in all but 3 patients, one of whom was later found to have a sequestrum. The failures were all in the group which was treated 48-hourly. In the larger group treated every 24 hours there were no failures. The swab was negative on the second day in about one-quarter of the infections and within a week in five-sixths.

The author recommends two preparations of penicillin for general use:

i. *Powder.* Sulphanilamide was used as a vehicle. The sulphanilamide, mixed with 5 % by weight of light magnesium oxide to prevent caking, was autoclaved at $1\frac{1}{2}$ atmospheres for 20 minutes, and when cold was shaken with penicillin powder to a final strength of 1,000 units of penicillin per gram. This was applied as a "frosting" to give a concentration of 4 units per cm.² of burn surface.

ii. *Cream.* Equal parts of soft paraffin, lanette wax SX and water were mixed at 60° C. and autoclaved in half-filled jars with the cap on at $1\frac{1}{2}$ atmospheres for 30 minutes. During cooling the cream was shaken several times. When cool, an aqueous solution of penicillin containing 500 units per cm.³ was stirred in, to make a final strength of 100 units per gram. This also was applied to the burn so as to give a concentration of 4 units per cm.² [A similar cream consisting of 30 % lanette wax in water has been found satisfactory in a warm climate.]

The cream was applied every 24 hours, or every 48 hours if the surface was relatively dry. The powder was used every 24 hours if a dry application was especially desirable, but it disappeared from the burn surface more quickly than the cream and appeared therefore to be somewhat less effective.

APPENDIX

THE OXFORD UNIT

The potency of penicillin preparations can at present be measured only by biological assay. Assay is carried out *in vitro* against a culture of a sensitive organism. As biological methods are subject to many variables it is necessary that each assay should be a comparative measurement against a standard of known potency. Early in the work at Oxford, for the convenience of workers inside the laboratory, a purely arbitrary penicillin standard was adopted by which the unit was defined as that amount of penicillin contained in 1 cm.³ of a certain buffer solution.

Dry preparations of partially purified penicillin have since been standardised against the original solution, and the "Oxford unit" (which has also been described as the "Florey unit") has been adopted as the standard of measurement by most workers in Britain, the U.S.A. and Canada. The potency of the unit is such that 0.01-0.02 of a unit per cm.³ inhibits the growth of ~~the~~ sensitive strains of the staphylococcus.

240

THE SLIDE-CELL TECHNIQUE

This technique was described by Sir Almroth Wright for measuring the bacteriostatic power of blood and serum. It depends on the fact that certain bacteria, particularly staphylococci, when planted in blood or serum in suitable numbers, will grow out as discrete colonies which can be counted under the low power of the microscope. In the original test (Colebrook, Storer & Wright, 1923) five narrow strips of paper about 0.1 mm. thick, which have been dipped in hot vaseline, are laid across a sterile microscope slide and another sterile slide is placed on top. This forms four chambers of a depth of about 0.1 mm. and a capacity of about 50 mm.³ The samples of blood or serum, mixed with suitable dilutions of culture, are run into the chambers and the ends are sealed with wax. After incubation the colonies are counted. Fleming has made much use of this technique in testing the

effects of antiseptics on bacteria and leucocytes. An example of its use in assessing the bacteriostatic power of the blood of patients undergoing penicillin treatment is given elsewhere.¹ It should be noted that serum, not whole blood, should be used in testing for antibacterial power due to penicillin as the erythrocytes take up less than 10 % of the penicillin in the blood (Rammelkamp & Keefer, 1943b)² and leucocytes, if present, would destroy some of the bacteria.

The modified test mentioned by Florey & Florey (1943)³ was designed to detect bacteriostasis in a single drop of the patient's serum. A measured drop (5-10 mm.³) is placed directly on one end of a sterile slide, which already bears a row of drops of the same volume of normal serum. Serial dilutions are made, the last drop of normal serum being left as a control. A small coverslip is put on to each drop and the edge is sealed with wax. After incubation the colonies are counted and the number is compared with that in the control. Where there is a fully bacteriostatic concentration of penicillin, no colonies develop.

¹ [see BMB 236]

² [see BMB 242]

³ [see BMB 233]

241

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242

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Readers of the *Bulletin* should note that supplies of penicillin are not at present available

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BRITISH MEDICAL BULLETIN

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No. 2

PULMONARY DISEASE

SPECIAL CONTRIBUTIONS

MEDICAL AND SOCIAL ASPECTS OF PULMONARY DISEASE by Dr. P. M. D'Arcy Hart	30
THE PRESENT POSITION OF CHEST SURGERY by Mr. R. C. Brock	33
RECENT WORK ON THE ANATOMY OF THE BRONCHI: WITH A DIAGRAMMATIC SURVEY by Dr. A. F. Foster-Carter	37

REVIEW OF SELECTED PAPERS

Applied Anatomy of the Lungs	
Bronchial Anatomy and Lung Abscess: I & II	39
Bronchial Embolism, Posture, and Lung Abscess	39
The Interlobar Fissure of the Lungs	40
Experimental Lung Damage	
Histology of the Isolated Perfused Lung	40
Healing of Experimental Lung Wounds	40
Dusts Causing Lung Disease	
Lung Tumours in Mice and Men	41
Failure of Aluminium to prevent Experimental Silicosis	42
Radiological Appearances in Coal Miners' Pneumokoniosis	42
Diagnostic Microscopy in Pulmonary Tuberculosis and Carcinoma	
Sputum Examination in the Diagnosis of Lung Carcinoma	42
Bacteriological Investigations in Mass Radiography	43
Laryngeal Swab Culture in Pulmonary Tuberculosis	43
Neoplasm and Cystic Disease of the Lung	
Surgery of Bronchial Carcinoma	43
Early Diagnosis of Pulmonary Neoplasms	44
Cystic Disease of the Lung	44
Therapeutic and Traumatic Collapse of the Lung	
Effect of Altitude on Pneumothorax	44
Observations on a Series of Cases of Internal Pneumonolysis	44
Pneumoperitoneum in Collapse Therapy	45
Surgical Treatment of Pulmonary Tuberculosis	
Persistence and Closure of Pulmonary Cavities	45
Extrascapular Apicolysis with Thoracoplasty	45
Results of Thoracoplasty	46
Closed Suction Drainage of Tuberculous Cavities	46
Drainage of Tuberculous Cavities—Technique and Indications	47
Artificial Bronchial Occlusion	47
Chest Surgery in Wartime	
War Injuries of the Chest	47
Early Treatment of Thoracic Injuries	47
Pathology of Closed Injuries of the Chest	47
Effect of Explosion Blast on the Lungs	48
Scope of Chest Surgery: Rehabilitation: Chest Radiography: Atypical Pneumonia	
Scope of Modern Chest Surgery	48
Rehabilitation of the Chest Case	48
Chest Radiography in Coryza and Sinusitis	49
Post-operative Radiography	49
Mass Radiography in Women	50
Mass Radiography at a Mental Hospital	50
Primary Atypical Pneumonia	50
Tuberculosis in Children	
Relation of Childhood Infection to Later Manifestations	51
A Hundred Cases of Tuberculosis in Children	51
Incidence of Tuberculosis in Children	51
Social and Statistical Aspects of Tuberculosis	
Tuberculosis in Peace and War	52
The Comprehensive Attack on Pulmonary Tuberculosis	52
Effect of War in Interval between Notification and Death	52
Survival Rates in Pulmonary Tuberculosis	53
Tuberculosis in London	53

BOOKS, MEMORANDA, REPORTS	54
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GUIDE TO THE JOURNALS	55
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This Number is devoted to a survey of recent investigations on pulmonary disease and its treatment or prevention by medical, surgical and social measures.

Dr. P. D'Arcy Hart, who contributes the first article, has been a member of the scientific staff of the Medical Research Council since 1937, and was previously Assistant Physician to University College Hospital. He was in charge of the medical part of the Council's investigation into chronic pulmonary disease in South Wales coalminers from 1937 to 1941, and is Secretary of its Committee on Tuberculosis in Wartime. The Report of this Committee is discussed in his article. During the past year he has been medical director in a team carrying out a mass radiography survey for the Council in selected population groups.

Dr. Hart has also been responsible for, or collaborated in, work on the value of tuberculin tests in man; on tuberculosis and social conditions; on tuberculosis in medical students; and on the pigments formed by streptococci. He gave the Milroy Lectures, Royal College of Physicians, in 1937, on "Prevention of Pulmonary Tuberculosis among Adults in England in the Past and in the Future."

Mr. R. C. Brock, who contributes an article on thoracic surgery, received his early training in this subject at Barnes Hospital, St. Louis, U.S.A., in 1930-31 as Fellow in Surgery and Assistant Surgeon to Professor Evarts A. Graham (to whom the Royal College of Surgeons of England has recently awarded an honorary Fellowship). In 1931 he was also attached to the Chevalier Jackson bronchoscopic clinic at Jefferson Hospital, Philadelphia, as clinical assistant to Dr. Louis H. Clerf. In 1934 he was appointed consulting

thoracic surgeon to the London County Council group of hospitals. He was appointed Assistant Surgeon to Guy's Hospital (where he is now Surgeon) and to the Brompton Hospital in 1936. The Brompton Hospital has been responsible for much pioneer work in thoracic surgery and is recognised as one of the leading chest surgery centres in the world. Its four surgeons perform over 1,000 chest operations there each year.

Mr. Brock is at present also one of a team at a special surgical chest unit in a large Emergency Medical Service Hospital which deals with wounded military and civilian patients, and certain classes of ordinary military and civilian surgical chest cases.

Dr. A. F. Foster-Carter, who contributes summaries in text and diagram, according to the most recent observations, of the anatomy of the bronchial tree and pulmonary segments, has been Resident Medical Officer at the Brompton Hospital since 1938. During the past 5 years he has been carrying out investigations on the anatomy of the lungs, and he has also published original observations on bronchial adenoma.

This Number contains two new sections, which will appear regularly in future. The first—"Books, Memoranda, Reports"—consists of short notes on medical publications not classified as periodicals. The second—"Guide to the Journals"—lists titles and authors of papers on clinical medicine and the medical sciences published in the United Kingdom. Many of the papers listed will subsequently be reviewed in the Bulletin.

It is hoped that these two new sections will serve to give the Bulletin a comprehensive character which it previously lacked.

SPECIAL CONTRIBUTIONS

243

MEDICAL AND SOCIAL ASPECTS OF PULMONARY DISEASE

P. M. D'ARCY HART, M.D., F.R.C.P.

Scientific Staff, Medical Research Council

growing interest in the social aspects of medicine, which lent in Great Britain, has been reflected in some inquiries published since the war, upon pulmonary disease. Among these, and one which owes its origin to the war conflict, is the Report of the Committee on Tuberculosis in Wartime (*Medical Research Council*, 1942a). The other major inquiry into the medical aspects of pulmonary diseases, published in Britain during the war, was begun several years before. This was a large-scale investigation by a team under the Committee on Industrial Pulmonary Disease of the *Medical Research Council*, on the problem of lung disease due to dust in the South Wales coal mines.

The Problem of Tuberculosis

The Committee on Tuberculosis in Wartime was set up by the *Medical Research Council* at the request of the Ministry of Health in order to inquire into the causes of the increase in tuberculosis, and to advise on remedies. It may be noted that in England and Wales the total tuberculosis deaths in 1941 exceeded the average of the years 1938 and 1939 by 3,000 (12 %), and that in Scotland the excess was 700 (20 %).

Findings and General Recommendations

The Report of the Committee emphasises as of primary importance the social background of tuberculosis, and the part probably played by the very complex, and in some respects radical, wartime alterations in national life in the rising tuberculosis mortality between 1939 and 1941. Some of these changes increased the risks of infection and others decreased the resisting power of the individual. Among them may be mentioned the black-out; overcrowding in homes due to destruction by bombing; movements of population due to evacuation; industrialisation of groups of persons not previously engaged in factory work; diminished resistance due to fatigue from long hours of work and travelling; and, in certain categories of persons, possible inadequate rations.

Some of these social factors operated in the last war (Greenwood & Tebb, 1919; Faber, 1938), but the present planned food policy has probably made nutritional deficiency a less serious factor, particularly in children. If anyone has

suffered it is most likely, according to the Committee, to have been adults, who were probably inadequately supplied with milk during 1940-1941. Young adults, especially young women, constitute a group particularly susceptible to environmental factors, so far as tuberculosis is concerned (Hart & Wright, 1939). In accordance with this analysis of social factors, the Committee recommends as of first importance "that continued watchfulness should be maintained upon the working conditions of young employees, particularly in regard to hours of work, transport difficulties, rest periods, factory canteens and hostel arrangements, and their relation to sickness absence."

Special Recommendations

The Committee's special recommendations, most of which have also strong social implications, fall under three main headings:

i. *Mass radiography.* Routine mass radiography is recommended with the double purpose (a) of detecting cases of tuberculosis in an earlier stage than has hitherto been achieved through the ordinary patient-doctor relationship, and placing them under treatment, and (b) of discovering unsuspected human sources of infection and removing them to safer surroundings for the benefit of the community as well as of themselves. The Committee advocates the use of the miniature method on which Abreu of Brazil did the pioneer work (Abreu, 1936, 1938, 1939), and which was further developed in various countries (Barros Barreto, 1937; Mazzei, 1937; Paula, 1938; Holfelder & Berner, 1938; Fournié & Frezouls, 1939; Berner, 1939; Ronneaux, 1939; Clark, Cordiner & Ellmann, 1941; Clark, Poulsson & Gage, 1941; Stanford, 1941; Stanford & Clark, 1942).¹ This method has proved successful during the present war in the Royal Navy (Dudley, 1941; Fitzpatrick, 1941; Brooks, 1943), in the Royal Air Force (Trail, 1942a, 1942b; Trenchard, 1943; Evans, 1943; Clive, 1943) and in the Australian Imperial Force (Cooper, 1940; Galbraith, 1941; White, 1941).

¹ [For fuller literature up to the war, see Bentley & Leitner, 1940.]

The Committee suggests that during the war priority should be given to groups in which young adults, particularly young women, are prominent, e.g. employees of war factories, nurses and medical students, merchant seamen. It is indicated that although the "diagnostic sweep" of a single mass radiography survey of a particular group will be useful, regular repetitions of such a procedure should in peace time be regarded as the best means of controlling the disease (Reid, 1940, 1941; Sawyer, 1941).

ii. *Financial provisions.* In Great Britain persons insured under National Health Insurance receive, when sick, a small weekly payment to help them during short periods of illness. This insurance was never intended to provide for the full support of sufferers from long-term illness requiring prolonged treatment, such as tuberculosis. Such persons, the Committee points out, often reach a very difficult economic position just when their needs are greatest; the result is too often a premature return to work, with consequent danger of relapse and of spread of the disease to others. The Committee recognises the very great importance of maintaining the standard of living of the tuberculous patient, both from the standpoint of helping in the conquest of his disease, and from that of enabling his family contacts to maintain their resistance, so reducing the chances of development of the disease among them. The Committee also realises that organisers of mass radiography will encounter the difficulty of persuading persons with tuberculosis, who may feel fairly well, to leave their work for treatment, because of the financial difficulties involved. To meet the special characteristics of tuberculosis the Committee recommends that a special money allowance be made for a definite period, e.g. one year at least, to all persons leaving work because of this disease, the amount to depend upon the needs of the patient and his family. This financial scheme, it is suggested, might be linked with a fund for providing payments to supplement, to their full amount, the wages of those returning to their employment on a part-time basis (see below).

iii. *Rehabilitation.* The tuberculous person, after he has reached convalescence (or, if a chronic case, the limit of benefit from treatment), is usually left to his own resources. He may fail to obtain work within his capacity and so be lost as a useful citizen; or he may plunge straight into full-time work, possibly of an unsuitable nature, and relapse. The Committee regards rehabilitation as an essential part of the treatment of tuberculosis, and suggests that arrangements should be made for the gradual return to industry of such persons on a basis of part-time or modified work. In considering the practicability of various kinds of re-employment, experience of different countries in this problem is drawn upon, e.g. that of Great Britain in Village Settlements, such as Papworth and Preston Hall, that of the U.S.A. in Municipal Work-Shop Schemes (Joint Tuberculosis Council, 1942), and that of the U.S.S.R. in methods of employment in normal industry (Vredenskaya, 1938, 1940; Gaft & Kalinin, 1940; Torkanovsky, 1940; Berenson, 1941; *British Medical Journal*, 1943). For the convalescent case in which cure is expected, it is suggested that a period of part-time ordinary work prior to resumption of full work will be adequate. On the other hand, in the chronic and perhaps infective cases, modifications or radical alterations in work may be required over long periods, and various types of collective arrangements to this end are outlined in some detail. Whether the work during rehabilitation be part-time or modified, or both, a financial supplement to wages is recommended in order that an adequate standard of living can be maintained by the patient and his family.

In scope and character this report goes far beyond proposals to deal with a wartime emergency. Indeed it represents an effort to obtain re-orientation of the attitude in Britain to the whole tuberculosis problem. This is to be achieved by a close integration of the social with the scientific medical approach.

Practical Measures

The Ministry of Health has responded by promptly implementing some of the main recommendations of the report. Thus, in December, 1942, the Minister announced (Circular 2741) that transportable miniature radiography sets, in accordance with a specification approved by the Committee's experts, would be made available for the use of a limited number of local authorities, the limits being set by the restrictions of war conditions on production and staffing.

These sets have been produced during 1943 and, at the time of writing, about half a dozen large local authorities have received them and at least 3 have commenced operations. A team under the *Medical Research Council* has meantime been carrying out field trials with one of the sets, and has surveyed employees of two large factories, the staff of a number of Government Departments, and the staff and patients of a large mental hospital; the results will be published shortly.

In April, 1943, the Ministry of Health issued a Memorandum (266/T) setting out a scheme for financial allowances for certain categories of persons leaving work to undergo treatment for tuberculosis. This scheme is now in general operation by local authorities, whose expenditure will be reimbursed by the State. It is expected that this scheme will be incorporated into any future scheme of social security of a general nature. Unfortunately it has not been possible to include any but pulmonary cases with good prospects of cure; non-pulmonary cases and the very large number of chronic pulmonary cases are excluded. Furthermore, the majority of wives in employment are excluded, whatever the type of their disease. An interesting feature of the scheme is that persons granted the financial allowances can continue to receive these, though on a reduced basis, if they have a period of part-time employment after treatment.

Allowances during part-time employment will probably prove to be one factor in promoting satisfactory restoration of the tuberculous to work. In addition, some at least of the recommendations of the Committee regarding more definitive arrangements for providing suitable work in normal industry or in special industries, with or without previous vocational training, are expected to find their implementation in the Disabled Persons (Employment) Bill now passing through Parliament.

In conclusion it may be stated that in 1942 there was a check in the wartime increase of tuberculosis mortality in Great Britain, though the number of new cases showed a further slight increase. The official view is wisely one of continued watchfulness and of warning against complacency, for in the last war a similar pause was followed by a resumption in the increase of tuberculosis deaths. The new developments discussed above should be of service in offsetting any tendency to deterioration, as well as in the long-term attack on this disease.

Industrial Pulmonary Disease

Reference was made in the opening paragraphs of this article to a comprehensive long-term investigation by a team appointed by the Committee on Industrial Pulmonary Disease of the *Medical Research Council*. The situation calling for such an investigation may briefly be summarised as follows: The number of miners certified as having silicosis for compensation purposes had been increasing yearly in South Wales relative to the whole country, and this increase was most marked in the anthracite area in the West; thus for the period 1931-37 the average annual number of new cases of certified silicosis per 1,000 underground workers was 5.23 in anthracite and 0.99 in non-anthracite mines in South Wales, as compared with 0.06 in coal mines in Great Britain excluding South Wales. Furthermore, it was believed by local doctors, as well as by the miners themselves, that other disabling conditions were being caused by dust besides that which was recognised as "silicosis" for compensation purposes.

Scope of the Investigation

The *Medical Research Council* inquiry was medical, including post-mortem studies, and environmental (*Medical Research Council*, 1942b, 1943). The medical inquiry was based upon a detailed examination of the men working at one colliery and on the more restricted examination of a selection of those in 15 other mines in South Wales, as well as a number of loaders of coal at 4 coal-shipping ports; a detailed study of 42 selected necropsy cases constituted the pathological part of this inquiry. The environmental survey dealt with the examination of the concentration, particle-size and chemical nature of the air-borne dust breathed by the collier at the coal face, the composition and characteristics of the strata from which the dust was derived, the temperature and humidity of the air, and the concentration of nitrous fumes derived from explosives; the mines studied were selected from those which formed the basis of the medical inquiry.

Summary of Medical Findings

The more important additions to knowledge resulting from the medical studies may be summarised:

i. *Description and classification of pulmonary changes.* A full description of the various pulmonary changes found is given, illustrated by photographs, and x-ray and pathological classifications are suggested. Tribute is paid to earlier classifications of coal miner's lung disease in Great Britain (e.g. Amor & Evans, 1934; Cummins, 1936; Cummins & Sladden, 1930), U.S.A. (e.g. Pancoast & Pendergrass, 1926; Bloomfield *et al.*, 1935), U.S.S.R. (Moshkovsky, 1941), Sweden (Edling, 1926) and other countries.

ii. *Topographical distribution of pulmonary abnormality.* The pulmonary abnormality encountered amongst South Wales coal miners is not restricted to the anthracite area, but can be found in the whole of this coal field. Its incidence and severity are greatest, however, among colliers who have worked for long periods at the coal face in the anthracite mines. Indeed, as indicated by recent coal mining compensation statistics, the main problem numerically in Wales is presented by the colliers, whereas in England the "hard-heading" workers (*i.e.* men who bore in rock) have been the main source of pulmonary trouble. This is not to say, of course, that such workers in South Wales coal mines escape, but there is not the same striking excess in the incidence over that in England.

iii. *Relationship between pulmonary abnormality and quality of coal.* A relationship is established between the incidence of pulmonary abnormality among the colliers, as judged by x-ray evidence, and the "rank" of the coal mined at the different collieries, though within the anthracite area there are also distinct local variations in incidence. The rank of coal in the South Wales coal field changes gradually from north-west, where the highest rank of anthracite is found, through the centre, where is the famous Welsh steam coal, to the south-east, where bituminous coal of the lowest rank in this field is situated. The incidence of pulmonary abnormalities among the colliers changes, broadly speaking, from high in the anthracite to low in the bituminous area, with a fairly gradual decrease between these two extremes. The presence of a low-incidence minority among the anthracite mines themselves appears to be associated with the presence of certain mines whose workings are relatively damp and shallow.

iv. *"Dust-reticulation."* The types of pulmonary abnormality in South Wales coal miners include a form of disabling pulmonary disease, due to dust inhalation, which does not come within the accepted definition of "silicosis" as used for the purposes of the Workmen's Compensation schemes. This condition is here named "dust-reticulation," partly because the x-ray appearance is that of a network without nodules, and partly because its pathological basis is a reticular-tissue response (the two-fold relevance of the term reticulation being of course a coincidence). Reticulation probably represents the first of a series of pathological changes which may culminate in the gross fibrosis found so often at autopsy, the latter corresponding to nodular and conglomerate shadows on the radiograph. The incidence of disability in men showing reticulation alone tends to be less than in those with the more advanced pulmonary abnormalities; it falls mainly on men in the second half of life.

v. *Differences in dust-induced pulmonary disease.* Both dust-reticulation, and the more developed nodular and conglomerate radiographic changes also seen typically in colliers, differ in several important respects from the pulmonary abnormality found characteristically in "hard-heading" workers (see ii. above), which corresponds closely to the silicosis occurring in persons exposed to high concentrations of quartz.

vi. *Pulmonary abnormality in dock workers.* The pulmonary abnormality shown to occur in colliers is found also to some extent in coal "trimmers" (*i.e.* coal boat loaders) working at the docks in South Wales, and among these may also give rise to disability which may prove fatal.

The report provides a full review of previous published work on lung disease due to dust in coal workers. It is interesting to note that the excess of trouble in anthracite mines over bituminous mines is not confined to South Wales but has been reported in contemporaneous investigations made both in the U.S.A. and U.S.S.R.

Summary of Environmental Findings

The principal findings of the environmental studies are as follows:

i. *Dust concentration and incidence of disease.* The incidence of pulmonary x-ray abnormalities among colliers at the different mines studied is positively correlated with the average concentration both of the coal and of the non-coal parts of the air-borne dust at the coal face, particularly as regards particles below 5 microns in size; this evidence confirms the generally accepted relation of the incidence of lung disease to the amount of dust inhaled.

ii. *Mineral analyses of dust and coal seams.* Chemical and x-ray diffraction analyses of the mineral matter in the coal seam and of the air-borne dust at the coal face are remarkable for their close similarity when derived from mines working widely differing ranks of coal. While the quartz amount varies, there is no clear relationship of this figure to rank of coal or to incidence of lung disease. Certain suggestive differences are, however, noted which may yield to deeper investigation, particularly if directed to the nature of silicates other than quartz in the coal seam.

iii. *Petrological studies.* Petrological examinations of the rock strata overlying the coal in different mines reveal a contrast between the shales in the anthracite and bituminous coal areas. Owing to the effects of compaction and metamorphism there are, in the anthracite area, an increase in the content of secondary quartz and mica, and a differentiation in the "ground mass," or ultimate cement substance, of the shale. Hydrated ferric oxide and alumina, both of which depress the solubility of silica, are less evident in the shales of the anthracite area than in those of the bituminous area. Whether directly or indirectly, the incidence of pneumoconiosis appears to be associated with these geological changes brought about by pressure.

Thus, while these environmental findings throw some light on the causes of variations in incidence of lung disease in different parts of the coal field, the striking relationship of the latter to the rank of the coals mined remains obscure and awaits further research.

Recommendations

From the practical standpoint the most important features of these inquiries lie in the recommendations of the Committee on Industrial Pulmonary Disease.

i. *Nomenclature.* The Committee recommends that the comprehensive term "pneumokoniosis of coal workers" should be used in future to cover "all the pulmonary conditions described as due to dust in workers engaged in any operation underground in coal mines, in screens workers at collieries and in coal trimmers at docks." This nomenclature is now being generally adopted in Great Britain.

ii. *Extensions of eligibility for compensation.* As dust-reticulation is clearly attributable to the industrial hazard and leads to some degree of disability, it is recommended that the diagnostic criteria required for purposes of compensation should be widened in scope, so as to include not only the more fully developed lung changes—as has hitherto been the case—but those established by the medical survey as comprising all the various stages of "pneumokoniosis of coal workers." The Workmen's Compensation Act (1943) embodies this suggestion, and in the summer of 1943 compensation began to be paid to miners with reticulation as well as to those with other forms of pneumokoniosis. Legislation to compensate coal trimmers, too (hitherto outside any scheme), may be expected in the near future.

iii. *Reduction of hazard.* The Committee makes certain recommendations for reducing the hazard in coal mines, particularly anthracite. These include: (a) improvement of ventilation; (b) all processes involving working in stone at the coal face to be carried out when the colliers are away; (c) shot-firing also to be carried out at a time when as few men as possible are present; (d) systematic use of water for dust-suppression to be exploited as fully as possible. Interesting developments can already be reported with regard to the last of these recommendations. Within recent months a method of infusing water into the coal face under pressure, before the coal is worked, has been introduced into certain mines in South Wales (Jenkins, 1943). The early results, which indicate a substantial reduction in the amount of dust produced, are promising, and further developments are eagerly awaited.

As with the tuberculosis report, the results of the pneumokoniosis inquiry should be felt for many years. We may hope that progress will be stimulated in a number of directions, e.g., in methods for the industrial rehabilitation and re-employment of men disabled by this intractable disease, in improved diagnosis by periodic mass

radiography coupled with physiological tests, in further methods for assessing the dust hazard and for suppressing the dust at the point of origin, and, indeed, in the general re-organisation of the national machinery for detecting and preventing industrial pulmonary disease among coal miners.

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THE PRESENT POSITION OF THORACIC SURGERY

R. C. BROCK, M.S., F.R.C.S.

Consultant Thoracic Surgeon, London County Council

Surgeon, Guy's Hospital and Assistant Surgeon to the Brompton Hospital, London

Before the war of 1914–18 very little thoracic surgery was being done except by a few bold pioneers, but the experience gained in the treatment of severe chest wounds served as a great impetus for its development. The influenza epidemics of 1917 and 1918 also led to big advances in the treatment of empyema and of lung-suppurations. The last 10 years in particular have seen the surgery of the thorax both widely accepted and widely practised, the most notable development being lung resection; pneumonectomy and lobectomy to-day are standard procedures, whereas before 1930 they were operations of rarity and hazard.

The surgery of the thorax is akin to neuro-surgery in the special training needed for its proper practice. It is not enough for a surgeon just to perform operations upon the chest as if he were a carpenter. He must possess a wide knowledge of the medicine and pathology of intrathoracic diseases as well as of the anatomy and physiology of the chest; he must be an expert bronchoscopist, able to form his own opinion on diagnosis and treatment, and must not

be guided entirely by his physician colleague. At the same time, close co-operation with a physician is essential for good work, and in no other disease is this so important as in pulmonary tuberculosis.

The medicine and surgery of any part of the body must rest, first of all, on a sound knowledge of anatomy. It is strange that until recently the anatomy of the bronchial tree has received but little attention, whereas a correct knowledge of the arrangement of the chief secondary bronchi is essential for a proper understanding of many lung diseases.

Lung Abscess and the Segmental Anatomy of the Lungs

Lung abscess has traditionally been treated conservatively, but the important part that surgery has to play in many examples of this serious condition is being increasingly recognised. A sound knowledge of the segmental anatomy of the lungs is essential both for prescribing correct postural drainage and for a correct and safe surgical approach for

open drainage. It is not satisfactory, in ordering postural drainage, just to tip the patient by raising the foot of the bed ; as was pointed out by Nelson (1934), a different position is needed for a lesion of different broncho-pulmonary segments. For instance, a patient with an abscess of the apical part of the lower lobe should lie prone.

Neuhof & Touroff (1936, 1942) have made important contributions in a consecutive series of articles in which they stress the importance of early drainage of the acute foetid abscess. These two surgeons have shown that all lung

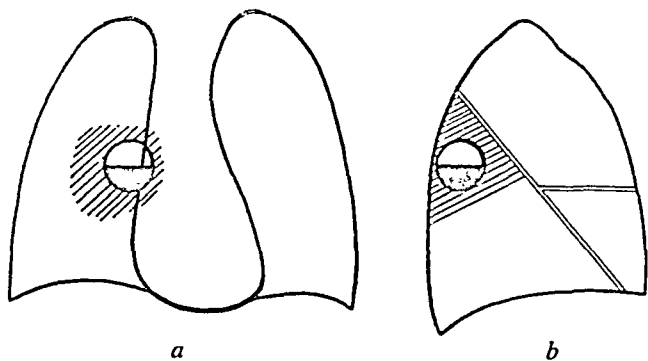


Diagram of abscess of the apical part of the right lower lobe. In the postero-anterior view (a) the appearance is that of a so-called "central" or hilar abscess. The lateral view (b) shows the true localisation, an abscess presenting on the visceral pleura at the periphery of the affected broncho-pulmonary segment.

abscesses approach the visceral pleura, the old conception of "central" and "peripheral" abscesses being false. This misconception has arisen from failure to use lateral radiographs, which are essential for the proper study of almost all lesions of the lungs and are indispensable in lung abscess. Early drainage of a lung abscess that is not showing prompt and steady response to conservative measures is associated with a low mortality and quick healing, with little or no residual damage to the lung. Delay for weeks, or even months, is most undesirable, for when operation is at last resorted to, the mortality is higher and permanent damage to the lung may be inevitable. In such cases lobectomy or pneumonectomy may be needed.

The aetiology of lung abscess is important and closer study of cases has shown that the old conception of the abscess following "pneumonia" is not correct. It rarely if ever follows an acute specific pneumonia, but is usually caused by a non-specific pneumonitis following the inhalation of infected material from bad teeth or during anaesthesia. This observation receives strong support from a correlation between the segmental anatomy of the lung, the sites most favoured by lung abscess, and demonstration that these sites are also those favoured by inhaled material in certain standard postures (Brock, Hodgkiss & Jones, 1942).

Empyema : Importance of After-Treatment

Empyema has long been considered the one chest disease which could be safely treated by the general surgeon. Although its widespread and common occurrence often necessitates treatment by the non-specialist, its management may leave much to be desired when it is not in the hands of a thoracic expert. It is fair to say that scarcely any other condition is treated so indifferently; instead of healing rapidly with no permanent disability, large numbers of patients are chronic sufferers or subject to recurrences lasting many months or years, require several operations, and end with permanent disability and deformity. In the past the surgeon has been content to evacuate pus by drainage at some convenient site and to leave in the drainage tube for an empirically determined time such as 10-14 days. It is uncommon to find any care expended on early mobilisation of the patient or on earnest instruction in breathing and postural exercises designed to encourage lung expansion and to prevent deformity. The thoracic expert knows only too well, from bitter experience with the many chronic empyema cases that come to him for treatment, that the greatest care and thought must be given to the correct placing of the drainage hole and to careful watching of the size, shape and extent of the healing pleural cavity. The tube, which may need frequent and patient readjustment, must be retained until the infected pleural space has been shown to be obliterated by complete fusion of the visceral and parietal pleurae; too

early removal of the drainage tube before the space has obliterated is the most frequent cause of chronic empyema (Brock, 1941). Allison (1943) has recently written a useful survey of the management of these cases.

The recognition of the importance of breathing and postural exercises is one of the big advances made in the treatment of diseases of the chest in the last 10 years. Perhaps the most striking difference between the "professional" and "amateur" thoracic surgeon is the use the former makes of this invaluable aid in the pre- and post-operative care of his patients. Unfortunately a chronic empyema still implies thoracoplasty to many surgeons, but most patients can be spared this further mutilation if proper drainage is instituted and maintained while vigorous physical treatment is given. Premature resort to the old mutilating Estlander and Schede operations is to be deplored. Only too often these operations are performed in cases in which the cause of the chronicity does not even lie in the pleura but in disease of the underlying lung, such as bronchiectasis, cystic disease, or growth. It is most important that every chronic empyema case should be completely investigated for the true primary cause of chronicity before treatment is decided (Brock, 1936).

Lobectomy and Pneumonectomy in Bronchiectasis

Bronchiectasis is a foul and loathsome disease causing much misery, suffering and death, and its surgical treatment was difficult and dangerous until the work of Brunn (1929) and of Shennstone & Janes (1932) gave us safe one-stage lobectomy with the tourniquet technique. Very soon large numbers of patients received the benefits of this operation, and in 1939 Tudor Edwards was able to publish his experiences in a series of 199 patients treated by lobectomy or pneumonectomy, the operative mortality being 12%. Among these cases were 38 children, aged 4-16, all of whom survived operation. Children tolerate lobectomy well and there can be no doubt that the disease is best treated in childhood if it is recognised then, for in addition to the low mortality from operation, the patient is spared the dangers and drawbacks of carrying his disease into adult life, often with stunting of stature and loss of much useful time from school or work. Churchill (1937) has also published a striking series of 49 cases in which the mortality was 6.1%, the last 30 consecutive cases being completed without a death.

Pneumonectomy soon followed lobectomy for bronchiectasis, the first operations being performed by Nissen (1931) in Germany and Haight (1934) in America. In Britain, Tudor Edwards and Roberts performed the first pneumonectomies for bronchiectasis by a one-stage operation in contrast to the two-stage procedure used by Nissen and Haight. The one-stage operation is now universally accepted.

The earlier tourniquet technique for removal of a lobe or a lung was of great value in establishing the operation, but for some years now it has given way to removal by dissection and ligation of the main vessels and bronchus, a procedure much more in keeping with sound surgical principles. Blades & Kent (1940) have written on the anatomy of the lobar vessels, as displayed at the dissection operation. Tudor Edwards originally performed a one-stage lobectomy for bronchiectasis by the individual ligation technique as long ago as 1929; this was the first successful case of its kind in Britain. Lobectomy has also been applied with great success to selected cases of bilateral disease and, finally, with the greater confidence that has followed knowledge of the anatomy of the broncho-pulmonary segments, even segmental resection of lobes has been successfully used.

The disability following lobectomy and pneumonectomy is usually small or non-existent. Greater disability may occur after pneumonectomy for carcinoma in an elderly patient, but even then any ordinary occupation can be followed. A successful lobectomy in a young patient should give rise to no disability whatever and many such patients are on full active duties in each of the fighting services to-day.

Surgery and Pulmonary Tuberculosis

The surgical treatment of pulmonary tuberculosis is a vast and increasing field of work. Some of the earliest pioneer work in the surgery of the chest rose from the treatment of this disease, and much steady progress has been made over many years. The problem has many important sociological and administrative bearings, apart from the pure surgical considerations, or more correctly, arising out of the success of surgical interference. Pulmonary tuberculosis remains a

great scourge in spite of its lessened incidence during this century and its victims are mostly young people. Apart from physical suffering and death, it brings with it much misery, deprivation and want, affecting the sufferer's family as well. Routine medical and sanatorium treatment play an invaluable and irreplaceable part, but far too many patients relapse afterwards and, as many reports have shown, of those who have a positive sputum at the end of sanatorium treatment some 75 % are dead within 3 years. Thompson (1943) has recently described an investigation of 406 adult patients followed for from 5-15 years in which the poor outlook for the patient with a cavity is emphasised. Thus, he found that 64 % were dead within 3 years and 75 % in 5 years.

There is much wastage from the policy of "patching-up" the patient with several months in a sanatorium and then sending him back to work, outwardly well, but inwardly still with uncontrolled, albeit temporarily silent, disease. The help of surgery is often requested only when years of chronic disease have had their effect. Many of the patients occupying the surgeon's time should have been operated upon two, three or more years before, and many others in the ideal phase for surgery are being sent back to work instead of to the surgeon. Village Settlements, such as *Papworth*, can play a useful part in the rehabilitation of a certain number of patients.

It is for this reason that the field of surgery in the treatment of pulmonary tuberculosis is potentially such a vast one, and will require considerable, preferably national, organisation to make it available for all who can benefit from it. If the number of sputum-positive cases sent back to their homes or to industry could be diminished, this alone would lessen the number of new cases.

The surgery of pulmonary tuberculosis is related chiefly to "collapse therapy," and in its simplest form begins with artificial pneumothorax. Air introduced into the pleura has itself no healing effect; it benefits the patient only when it enables the diseased part of the lung to relax. For this reason it is inevitable that thoracoscopic division of adhesions limiting collapse of the lung must play a very important part in treatment. This operation, performed skilfully, carries a low morbidity and mortality. Barclay (1943) has recently written of his experiences in 80 cases; previously Chandler (1937) has recorded his experiences in 210 operations, and Brock (1938a) has written of his results in 442 operations with the low incidence of 5 cases of simple tuberculous empyema and 5 cases of empyema with mixed infection—many times lower than that of artificial pneumothorax cases left with adhesions undivided. In other words, the incidence of complications is lessened by cauterisation of adhesions. The last of the papers mentioned above also contains a complete account of the technique of the operation and a practical consideration of the structure of adhesions. Just as every sanatorium or hospital treating phthisis should be equipped for pneumothorax treatment, so should it have facilities for division of adhesions in suitable cases.

A few years ago extrapleural pneumothorax had a phase of great popularity (Roberts, 1938; Brock, 1938b; Sellors, 1938), but to-day it is seldom used. It is an operation of value in a few carefully selected cases, chiefly in children below 16 years of age, and in older patients with an acute lesion unlikely to be controlled by rest alone, and in whom an ordinary pneumothorax has failed. The operation has a mortality (10 %) and a morbidity too high for general use; only about one-half of the patients derive substantial benefit from it, and this is too low a figure for an operation of election. If the patient is fit for a thoracoplasty, or is likely to become fit enough after a proper period of rest, then extrapleural pneumothorax should never be used in its place.

Thoracoplasty is a good operation with a relatively low mortality and morbidity and gives a high percentage of permanent cures. As stated above, if it could be used more often on earlier cases, the results would be even better.

Until some 6-7 years ago thoracoplasty consisted essentially of resection of the ribs, a method which gave only lateral compression of the lung. In 1935 Semb, following on the work of his senior Holst, introduced extrafascial apicectomy by which the diseased part of the lung is mobilised by deliberate and careful dissection so as to give the concentric relaxation and collapse that can otherwise be obtained by a perfect artificial pneumothorax (Semb, 1935, 1937). Semb's operation is now almost universally accepted and practised

and is a great advance in the surgical attack on phthisis. Thomas & Cleland (1942, 1943) have recently written fully of their experiences with the operation and of their results.

Overholt (1941) has recorded the results of his team in which the mortality from operation in 874 patients (a total of 1898 operations) was only 5.3 %, and 5 years or more later 94 % of the patients were alive and well, with the disease arrested; 83 % were working.

The importance of submitting suitable patients for operation early and not delaying until the "slipping chronic" stage has been reached is emphasised by Freedlander & Wolpaw (1937), who compared the results of operation upon 85 patients with a control group of 58 patients who refused operation. Thoracoplasty gave good results in 75 % of the "good chronic" cases and in only 57 % of the "slipping chronic" group. Hurford (1941) in a similar but smaller investigation found that of 54 unfavourable cases, 65 % were satisfactory after at least one year, whereas of 44 controls who had refused operation, 45 % were dead; of the thoracoplasty patients surviving, 64 % were working.

While collapse therapy is the essence of the surgical treatment of pulmonary tuberculosis, cases still remain in which a cavity in the lung does not respond to the standard measures. The problem of the mechanism of the production of cavities has stimulated much investigation (Coryllos, 1936; Coryllos & Ornstein, 1938; Goldman, Brunn & Ackerman, 1941; Thomas, 1942), but the name of Monaldi (1939) is particularly associated with the proposal of treating a certain type of "distension" cavity by constant gentle suction through an indwelling catheter used for drainage. The method has taught us much of the physiology and pathology of cavities but has been disappointing in its results. Like extrapleural pneumothorax, it has a very limited application, chiefly for a few early or bilateral cases. Sellors (1942) finds that thoracoplasty is still needed in most of the patients on whom it is used. Maxwell & Kohnstamm (1943) also find the end-results disappointing. Both the last-named papers contain much valuable information on the technique and management of the treatment of cavities by the Monaldi method.

The chief difficulty in the way of permanent closure of the cavity seems to be persistence of the bronchial fistula. If it were possible to close the bronchus safely and easily it would be a big advance. Thomas, Gough & Still (1943) describe the use of plasma-clot for this purpose and show that there is a field for investigation into similar methods.

Pneumectomy in Bronchial Carcinoma

The most striking advance in the surgery of the chest during recent years lies, undoubtedly, in the attack on bronchial carcinoma. Scarcely 10 years ago a diagnosis of bronchial carcinoma was the equivalent of a death-sentence, for the only form of treatment then available, deep x-ray therapy, has probably never cured a genuine case of the disease. The success attending lobectomy for bronchiectasis led to the use of the operation for favourable cases of carcinoma, but with only limited success, for the number of cases which could be treated in this way was small and the recurrence rate was high. In 1933, however, Graham was able to report his dramatically successful case of one-stage pneumonectomy for carcinoma; the patient, a physician, was still alive and well more than 10 years after. This operation was a modified tourniquet resection, but later in the same year Rienhoff performed the first pneumonectomy by dissection, and since then he and Overholt have published numerous papers on their experiences. Dissection pneumonectomy with removal of the adjacent mediastinal glands has now become the accepted standard surgical procedure for operable cases of bronchial carcinoma and is an operation based on those same sound principles which have proved so successful in the surgical treatment of carcinoma of the breast and colon. Overholt (1940) in a survey of his own series and 58 from a special questionnaire has shown that the results are promising, that they are far better than those of deep x-ray therapy or of any other method of treatment, and have fully justified the operation. In this country Brock (1943) has recently published an account of his experiences in which the operability rate in 187 consecutive cases was 8 %, and of his results in radical removal in 29 patients.

The main problem to be solved in pneumonectomy is successful primary healing of the divided bronchus. This still causes great difficulties, but much useful experimental

and clinical work has been published on it (e.g. Rienhoff *et al.*, 1942). Brock has obtained good results by the use of a pedicled intercostal muscle graft for the closure, but his work has not yet been published. It is probable that no method will ever ensure primary closure in every case, just as it is at present impossible to ensure primary healing of all wounds in the body. Sepsis is present in many cases of pneumonectomy, and breaking-down of the suture line is inevitable at times. Nevertheless there is still room for improvement, and few will contest that a great impediment to smooth and easy convalescence will be removed when the problem of the safest method of bronchial closure is solved.

Radiology and Anæsthesia : Future of Thoracic Surgery

The present firm position of thoracic surgery rests on two other things, besides its intrinsic strength ; these are radiology and anæsthesia. Without radiology no precision would be possible and no decision would be safe. Until Roentgen's discovery the time was not ripe for the development of thoracic surgery, especially the surgery of pulmonary tuberculosis. The invaluable part played by radiology in the complex post-operative care is ably surveyed and illustrated by Cleland & Rackow (1943).

No thoracic surgeon would deny to the modern anæ-

thetist full acknowledgment of the invaluable part played by him in the success of the severe and formidable operations of pneumonectomy, lobectomy, thoracoplasty, and thoracotomy for the removal of mediastinal tumours. While the surgeon opens the chest and operates upon the viscera therein, often producing profound interference with their function, respiration and circulation must be maintained and the anæsthetist is faced with many problems in achieving this. Local anæsthesia has made thoracoplasty easier and safer; controlled respiration (Crafoord, 1938, 1940; Nosworthy, 1941) has done much to help open thoracotomy and lung-resection. Nosworthy in particular has written fully and clearly on the problems of anæsthesia in intrathoracic surgery. Just as thoracic surgery itself is still advancing, so its two able supporters, radiology and anæsthesia, are constantly improving.

Many difficult problems in connection with the lungs have been solved, problems which a few years ago seemed insoluble. Less great but none the less worthy progress is also being made in the surgery of those two other most difficult and resistant organs, the œsophagus and the heart. The next ten years will probably see just as great advances in the solution of their surgical problems as the last decade has seen in the surgery of diseases of the lungs.

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¹ [see BMB 263]

² [see BMB 259]

³ [see BMB 249]

⁴ [see BMB 278]

⁵ [see BMB 269]

⁶ [see BMB 268]

⁷ [see BMB 265]

⁸ [see BMB 266]

⁹ [see BMB 267]

¹⁰ [see BMB 270]

¹¹ [see BMB 288]

RECENT WORK ON THE ANATOMY OF THE BRONCHI

A. F. FOSTER-CARTER, D.M., B.Ch.

Resident Medical Officer, Brompton Hospital, London

[This article should be read in conjunction with the diagrams on the next page]

Apart from the researches of a few workers at the end of the nineteenth century, notably Aeby (1880), William Ewart (1889), and Narath (1901), the anatomy of the bronchi received comparatively little attention until the last decade. The introduction of bronchoscopy, the development of chest radiography, particularly bronchography, and the advance of thoracic surgery have caused a revival of interest in bronchial anatomy, and many papers on this subject have now been published. Ewart was the first to notice that each branch-bronchus supplies a definite area of lung, and these areas have since been called the "broncho-pulmonary segments." In 1932, Nelson pointed out that the apex of the lower lobe could be regarded as a separate entity having its own bronchial and blood supply, and in the same year Kramer & Glass (1932) published a description of all the broncho-pulmonary segments. Later, Nelson (1934) gave a concise description of the distribution of the bronchi, which has been widely accepted.

Certain French workers have also published descriptions of the bronchi and segments, notably Grandgerard & Weber (1935) and Lucien & Weber (1936), and a summary of their researches has been given by Hovelacque, Monod & Evrard (1937). Churchill & Belsey (1939) described the anatomy of the "lingula" of the left upper lobe, and Neil, Gilmour & Gwynne (1939) have also given an account of the bronchi and segments. The surgical anatomy of the lung roots has been described by Hovelacque, Monod & Evrard (1937), and by Kent & Blades (1942), and those interested in the histology of the bronchi and lung should consult Miller (1937).

Foster-Carter (1942) has shown that previous accounts of bronchial anatomy contained certain inaccuracies and has given a detailed account of the bronchi with particular reference to those of the right upper lobe which were incorrectly portrayed in the past. More recently Brock (1942) has corroborated this description of the right upper lobe. The following account of the human bronchial tree is based on the study by the writer of celloidin casts, dissections, segmental injections, and bronchograms. The simplest possible names have been used, and the series of explanatory diagrams will help to make the description clear; the letters in square brackets refer to the diagrams.

It is convenient to regard the bronchial system in each lung as a stem with a series of branches, and there is sound embryological justification for this conception (Huntington, 1920). The first or eparterial branch of the right stem-bronchus [d] is directed laterally and supplies the right upper lobe. It divides into three branches, anterolateral or ventral [e], posterolateral or dorsal [f] and apical [g]. Many previous accounts have mentioned a fourth or "axillary" branch, but this does not normally exist in the human lung (Foster-Carter, 1942). The axillary area is supplied by lateral branches from the anterior and posterior divisions and not by a separate axillary branch. The apical bronchus also sends a branch to the upper part of the axillary area. The next branch of the right stem-bronchus, the middle bronchus [h], is directed forwards and supplies the right middle lobe; it has two principal divisions, lateral [k] and anterior [m].

In the left lung, the branch to the upper lobe combines the functions of the eparterial and middle bronchi on the right. The left upper lobe is equivalent to the right upper and middle lobes, and is sometimes subdivided by a fissure.

The left upper bronchus [s], therefore, has two main divisions: the left ascending bronchus [u] and the left middle bronchus [t]. The ascending branch is equivalent to the eparterial bronchus on the right and has similar branches—anterolateral, posterolateral and apical—the last two arising by a common stem, which the writer has called the apico-posterior [v]. The left middle bronchus [t] supplies the lower part of the left upper lobe, which is equivalent to the right middle lobe and is often called the "lingula"; it has anterior [m] and lateral [k] divisions resembling those of the right middle bronchus.

The bronchi of the two lower lobes are similar and may be considered together. After the stem-bronchus enters the lower lobe, the first branch is the dorsal bronchus [n] directed backwards. This supplies the apex of the lower lobe, and its branches can extend outwards as far as the posterior axillary line and downwards as far as the 10th thoracic vertebra on the inner side. The next branch, the cardiac bronchus [o], is peculiar to the right lung; it arises from the medial aspect of the stem and supplies the medial part of the right lower lobe adjacent to the heart. A short distance further down, a large branch, the anterior basic [p], arises from the anterolateral aspect of the stem to supply the anterior part of the lower lobe. The stem-bronchus then appears to divide into two terminal branches, the lateral basic [q] and the posterior basic [r]. These supply the lateral and posterior parts of the lower lobe, and the posterior basic branch is actually the direct continuation of the stem-bronchus itself.

Figures 4 to 9 show the areas of lung (broncho-pulmonary segments) supplied by the branches described above. The size of each segment varies slightly in different lungs, but the segments, like the bronchi, are fairly constant in position. In this account, an attempt has been made to depict the most common arrangement of the bronchi and their segments, and this pattern, with very slight variations, will be found in the majority of instances.

It is necessary for both physician and surgeon to have a working knowledge of the bronchial tree and broncho-pulmonary segments upon which to base their diagnosis and treatment of thoracic disease. For instance, in the interpretation of bronchograms it will be seen that the most complete survey of the bronchi is obtained by outlining those of each lung separately and then taking both antero-posterior and lateral radiographs [Figs. 1, 2 & 3]. If the bronchi of both lungs are outlined at the same time they become superimposed in the lateral view and the only way to separate them is to take an oblique radiograph with the chest at an angle of 45 degrees to the x-ray film [Figs. 10 & 11]. Pathological processes, particularly lung abscesses, tend to involve one or more broncho-pulmonary segments, and the importance of a knowledge of these subdivisions to the thoracic surgeon has been clearly shown by Brock (1942; 1943). The physician, also, when planning the postural drainage of a suppurative lesion in the lung, must first decide from the x-ray which segments are involved, and then place the patient in such a position that the bronchi draining these segments are dependent (Nelson, 1934; Foster-Carter, 1943). For instance, a lesion in the apex of the lower lobe [n] is best drained by placing the patient in the prone position, while one in the middle lobe area [m] will drain most efficiently if he lies on his back.

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 * [see BMB 248]

¹ [see BMB 247, 249, 250].

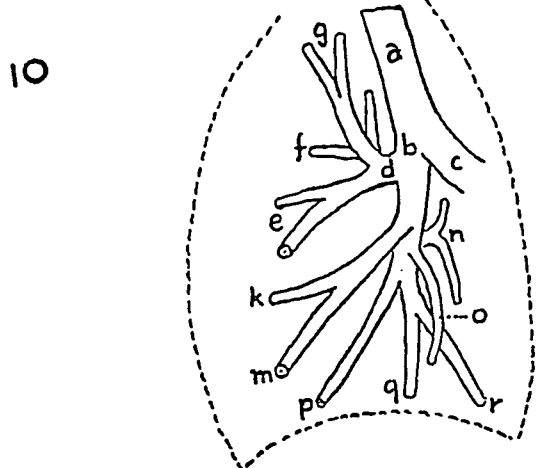
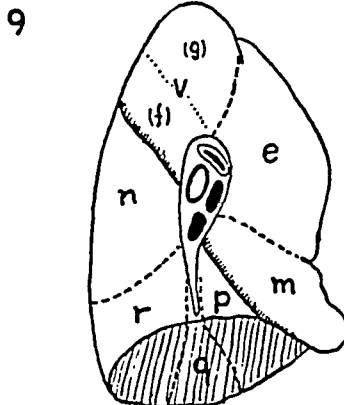
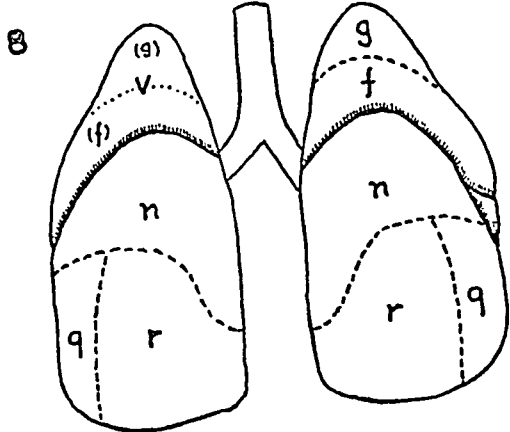
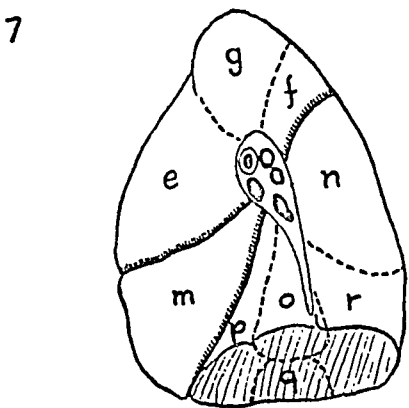
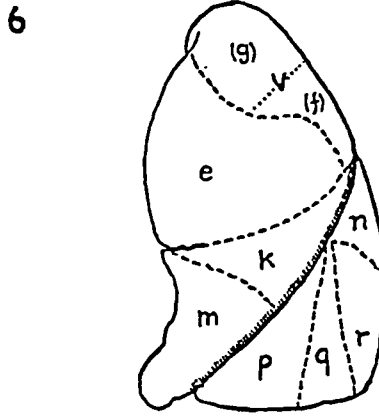
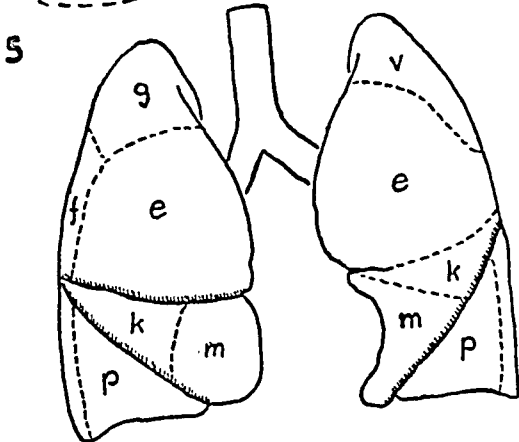
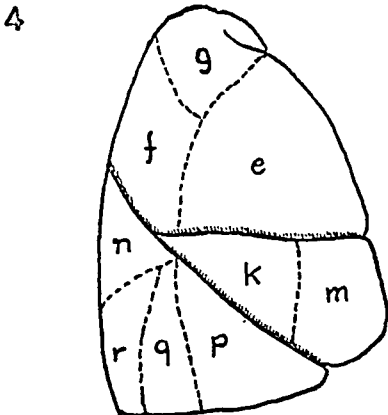
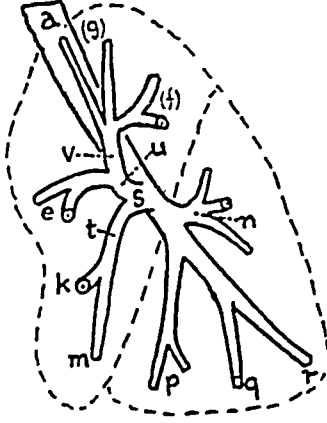
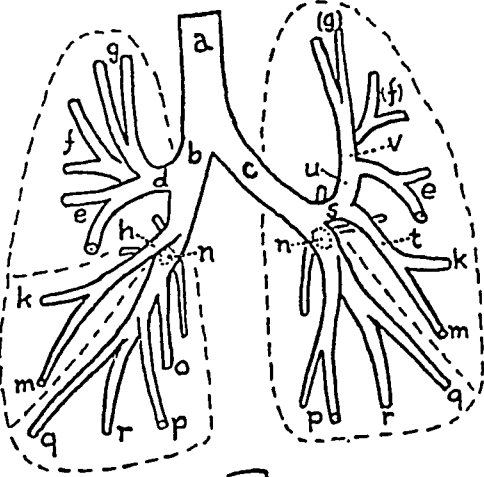
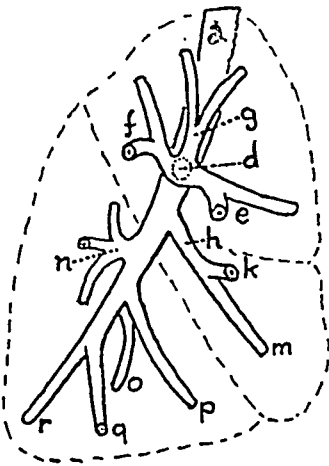
SUMMARY IN DIAGRAM OF THE ANATOMY OF THE BRONCHI AND BRONCHO-PULMONARY SEGMENTS

[These diagrams have been drawn for British Medical Bulletin by Dr. A. F. Foster-Carter. They should be studied in conjunction with the article on the preceding page.]

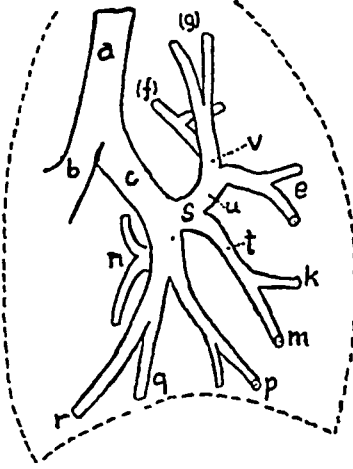
- 1. Bronchial Tree, right lateral view.
- 4. Right Lung, lateral view.
- 7. Right Lung, medial view.

- 10. Bronchi of Right Lung, left anterior oblique position.
- 2. Bronchial Tree, anterior view.
- 5. Both Lungs, anterior view.
- 8. Both Lungs, posterior view.

- 3. Bronchial Tree, left lateral view.
- 6. Left Lung, lateral view.
- 9. Left Lung, medial view.
- 11. Bronchi of left lung, right anterior oblique position.



11



Key to the Bronchi and Segments

- a. Trachea.
- b. Right main bronchus.
- c. Left main bronchus.
- d. Eparterial (right upper).
- e. Anterolateral.
- f. Posterolateral.
- g. Apical.

- h. Right middle.
- k. Lateral middle.
- m. Anterior middle.
- n. Dorsal.
- o. Cardiac.
- p. Anterior basic.
- q. Lateral basic.

- r. Posterior basic.
- s. Left upper.
- t. Left middle (lingula).
- u. Ascending.
- v. Apicoposterior.
- (1) Posterolateral and Apical branch.
- (2) of the Apicoposterior bronchus.

REVIEW OF SELECTED PAPERS

Applied Anatomy of the Lungs

247

BRONCHIAL ANATOMY AND THE SURGERY OF LUNG ABSCESS

by R. C. Brock, *Guy's Hospital Reports*, 91, 111-130, 1942

This paper deals with the surgical treatment of abscesses in the right upper lobe. The author stresses that it is essential for the surgeon to have a knowledge of the anatomy of this area and he gives an illustrated description of the branches of the eparterial bronchus which agrees with that of Foster-Carter (1942).

The segment most often involved in a lung abscess is the posterolateral, which occupies the paravertebral part of the right upper lobe below the apex, and extends to the posterior part of the axillary region. The apical and anterolateral segments are less common sites for suppuration. In planning the treatment of an abscess in the right upper lobe, it is essential to study both antero-posterior and lateral radiographs and to remember that a true axillary abscess is rare; an abscess in the axillary area is usually situated in either the posterior or the anterior part.

An abscess may present on the interlobar fissure, which will then show a smooth downward projection in the lateral radiograph. Rupture of an abscess into the fissure produces a characteristic globular or ovoid opacity due to the formation of an interlobar empyema, and this may be mistaken for the abscess itself.

The author advocates the early drainage of lung abscesses and stresses that this must be preceded by very accurate localisation, based upon a knowledge of the segmental anatomy of the region involved. Good antero-posterior and lateral radiographs are the first essential and the position of the most favourable point for drainage, namely the point at which the abscess is nearest to the surface, must be checked by measurement against a fixed landmark such as the sternum in both views [see also Cleland & Rackow, 1943]. If the primary segment involved can be ascertained, but the actual abscess is obscured by surrounding pneumonia, it is often possible to drain it successfully at the site of election for that particular segment. The injection of a small quantity of iodised oil mixed with methylene blue into the intercostal tissues over the suspected site is sometimes useful, as it provides a landmark which is visible both in the radiograph and at operation. Bronchoscopy is also of value in localisation; pus will often be seen exuding from the bronchus which drains the affected segment.

Most abscesses of the right upper lobe are best approached through an incision in some part of the axilla. An anterior approach is necessary occasionally, but should be avoided if possible as it tends to produce an ugly deformity. A paravertebral abscess must be drained from the back. Abscesses in the apical segment are uncommon. When they occur, an axillary approach and resection of part of the 3rd rib will usually give dependent drainage.

An abscess of the anterior part of the anterolateral segment will usually have to be drained from the front, and it commonly lies beneath the anterior end of the 3rd rib. The lateral part of the anterolateral segment normally lies beneath the 3rd rib just anterior to the mid-lateral line, and this is the site of election for drainage.

The posterolateral segment is the most common site for an abscess in the right upper lobe. In the lateral radiograph this region is often obscured by the shoulder girdle, and localisation of the lesion may be difficult. Every effort should be made to decide whether the abscess involves the posterior or lateral part of the segment, or both. A paravertebral abscess, in the posterior part, is best drained from the back; it usually lies under the posterior ends of the 4th or 5th ribs and the resection may have to extend back as far as the transverse processes of the vertebrae. An abscess in the lateral part of the posterolateral segment, or one which involves the whole segment, is best drained by resection of part of the 3rd rib high up and far back in the axilla.

Multiple abscesses may necessitate drainage at more than one of these sites simultaneously.

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- ² Foster-Carter, A. F. (1942) *Brit. J. Tuberc.* 36, 19
- ¹ [see BMB 278] ² [findings summarised in BMB 245]

248

BRONCHIAL ANATOMY AND THE SURGERY OF LUNG ABSCESS. Part II

by R. C. Brock, *Guy's Hospital Reports*, 92, 26-37, 1943

In this paper the author first deals with the surgical anatomy of the left upper lobe. [His description agrees with that given in BMB 245 except for the exact distribution of the subdivisions of the lingula or left middle bronchus.] He considers that the lateral division of the left middle bronchus extends forwards above the anterior division, so that the corresponding segments should be called upper and lower rather than lateral and anterior. Nevertheless, he states that there is an important lateral branch from the upper division which contributes to the "axillary area" of the left upper lobe. This area is supplied by lateral branches from the anterolateral, posterolateral, and left middle (lingula) bronchi, and is a common site for the formation of an abscess. Brock shows that all these branches are dependent when the subject lies on the left side, and suggests that left axillary abscesses are usually caused by the aspiration of infected material when lying in this position.

The lower or anterior branch of the lingula is of particular importance in bronchiectasis, as it is often involved together with the bronchi of the lower lobe, and then has to be resected when performing a left lower lobectomy. Lee Lander & Davidson (1938) showed that infected emboli from the main bronchus would tend to be aspirated into the left middle bronchus as well as the lower lobe, because of the downward direction of this branch. Brock points out that, for the same reason, when the patient is in the upright position, secretions filling the lower bronchus can spill over into the lingula.

The left apical segment is rarely the site of a lung abscess; the best surgical approach to it would be through the 2nd or 3rd rib, high up and far back in the axilla. Abscesses of the left posterolateral segment can best be reached from the back by resection of the 4th or 5th rib close to the spine. The anterolateral segment is the most common site for suppuration in the left upper lobe, and its lateral or axillary part is most often affected. An abscess in this area should usually be drained in the mid-axilla and the exact level must be carefully determined by radiography as described by Brock (1942). The lateral or axillary part of the lingula is also a common site for suppuration; an abscess in this segment may be indistinguishable radiologically from one in the lateral part of the anterolateral segment, and it is treated in the same way. Abscesses in the anterior parts of the anterolateral or left middle segments usually approach the surface on the anterolateral aspect of the chest, and the best position for drainage is again determined by accurate localisation of the area involved.

The original paper is noteworthy for the profusion of its excellent illustrations.

REFERENCES

- ¹ Brock, R. C. (1942) *Guy's Hosp. Rep.* 91, 111
- Lee Lander, F. P. & Davidson, M. (1938) *Brit. J. Radiol.* 11, 65
- ¹ [see BMB 247]

249

BRONCHIAL EMBOLISM AND POSTURE IN RELATION TO LUNG ABSCESS

by R. C. Brock, F. Hodgkiss & H. O. Jones, *Guy's Hospital Reports*, 91, 131-139, 1942

The authors quote a number of published accounts to show that a lung abscess is usually confined to one lobe and

occurs more often in the right lung than in the left. They are of the opinion that most lung abscesses are due to the inhalation of infected material, probably during sleep when the patient is lying down. Basal abscesses are common after abdominal operations because the patient is nursed in a sitting position, but the upper lobes are frequently the site of suppuration after other operations, such as those on the nose and throat, when the patient is nursed lying down.

The authors show radiographically that small quantities of iodised oil injected into the trachea, when the patient is lying on his right side, usually reach the posterolateral area of the right upper lobe. This is of particular interest in view of the frequency of suppuration in this segment. When the patient lies on his back, oil from the trachea usually runs into the right first dorsal bronchus supplying the apex of the right lower lobe; it may also enter the posterolateral segment of the right upper lobe and less frequently the apex of the left lower lobe.

The authors point out that these two areas into which oil from the trachea tends to be aspirated, the posterior part of the right upper lobe and the apex of the right lower lobe, are common sites both for a lung abscess and for tuberculous lesions. They suggest that both these conditions may be due to the aspiration of infected bronchial emboli from the upper respiratory tract.

250

THE INTERLOBAR FISSURES OF THE LUNGS

by R. C. Brock, *Guy's Hospital Reports*, 91, 140-146, 1942

The author is of the opinion that the posterior end of the main fissure is at a lower level than is commonly supposed. Many textbooks of anatomy give the upper level of the main fissure as the posterior end of the 4th rib or the spinous process of the 3rd dorsal vertebra. An abscess in the apex of the lower lobe would therefore be expected to lie deep to the 3rd to 6th ribs posteriorly. This is not the case, and the correct level to drain such an abscess is usually at the 8th rib. Bronchograms rarely show the apex of the lower lobe at a higher level than the 5th to 6th rib, and this is probably the normal upper limit of the main fissure of the right lung. The fissure of the left lung sometimes reaches the level of the 4th or even the 3rd rib. In the original paper, illustrations are given of a dissection of the thorax showing the pulmonary fissures, together with radiographs taken after metal strips had been placed in the fissures.

Experimental Lung Damage

251

THE HISTOLOGY OF THE ISOLATED PERFUSED LUNG

by O. A. Trowell, *Quarterly Journal of Experimental Physiology*, 32, 203-212, December 1943

In this paper from the Physiology Department of the University of Edinburgh the author describes histological changes in isolated dogs' lungs, which were perfused with heparinised blood under negative-pressure ventilation for a period of 3½-7 hours. A total of 34 lungs was examined in 20 perfusions (by the technique of Daly, Hebb & Petrovskaja, 1941). The lungs of 5 normal dogs served as controls.

From each lung three samples were removed, fixed and stained. The author summarises some of the histological features of the normal dog lung and refers to differences in other species. The constant histological changes seen in the perfused lung were (i) oedema manifested by alveolar exudate, distension of periarterial lymphatics and oedema of arterial walls; (ii) periarterial and peribronchial hæmorrhage, which could also be seen on macroscopic examination; (iii) accumulation of polymorphonuclear leucocytes in small blood vessels, often entirely filling the lumen of the venules. (The disappearance of polymorphs from blood perfused through the isolated lung was observed but not published by R. G. Bickford & F. R. Winton in 1934. Further observations on this point will be reported elsewhere in detail by the present author. The extent of accumulation of polymorphs in some of the small vessels is sufficient to account for their disappearance from the circulating blood); (iv) dilatation of

bronchi and bronchioles with smoothing of the normal convolutions of the bronchial epithelium. Appearances suggested loss of tone or reactivity of bronchial muscle (the bronchial circulation was not perfused); (v) vascular congestion of bronchial walls, except where outflow from the pulmonary veins was allowed.

The three main changes described—oedema, periarterial hæmorrhage, and intravascular accumulation of polymorphs—were never evenly distributed, nor did the various changes necessarily occur in association. Bronchial dilatation and congestion were always uniformly distributed when present.

The author reviews the findings of other workers on histological changes after acute oedema and certain types of experimental lung damage. From the reports of these other workers it is evident that the main pathological features of the perfused lung are also found in other types of lung damage, and the author suggests that such changes represent a common reaction to pulmonary trauma. He regards increased capillary permeability as the chief cause of oedema, and rupture of the vasa vasorum as the chief cause of periarterial hæmorrhage. Bronchial congestion was presumably due to some obstruction of the veins draining the bronchial tree.

REFERENCE

Daly, I. de B., Hebb, C. O. & Petrovskaja, B. (1941) *Quart. J. exp. Physiol.* 31, 129

252

HEALING OF EXPERIMENTAL WOUNDS OF LUNG

by G. L. Montgomery, *British Journal of Surgery*, 31, 292-299, January 1944

Little information is available on the process of healing wounds of the lung. The author has experimentally investigated this problem at the *Wilkie Surgical Research Laboratory*, Edinburgh. Triangular sections of lung were excised, under endotracheal ether anaesthesia, from 17 adult cats. Wounds were sutured in layers, and the cats recovered quickly and seemed little disturbed by the procedure. They were killed at intervals of from 36 hours to 115 days after operation, and sections of lung at the site of excision were made for study of the histological appearances in different stages of repair.

i. *Reconstitution of the continuity of the pleura.* The pleural limiting membrane was reformed by the cells of the superficial alveoli of the lung. This proliferative change was followed by the production of hyperplastic cells which appeared to originate from the capillary endothelium of the alveolar walls. Fibrin from blood clot deposited on the interrupted pleural surface appeared to stimulate proliferation of remaining serosal cells. Both alveolar endothelium and pleural serosal cells appeared to give rise to the fibroblastic tissue external to the limiting membrane of the lung. The elastica of the pleural membrane developed in the new collagen barrier.

ii. *Regeneration of the lung.* Evidence of regeneration was seen at a very early stage. The most important change was the development of new bronchial buds from the bronchi. These first appeared as cubical cells replacing the columnar ciliated epithelium. Later, cubical cells appeared external to the membrana propria, and at a further stage narrow channels of cubical epithelium developed. This proliferation occurred on the aspect of the bronchus directed towards the wound. The bronchial buds increased in number and size, and muscle fibres and elastic tissue appeared in their walls. At a later stage of regeneration, the lining of the new bronchial ramifications reverted to the columnar ciliated type of epithelium. Cubical epithelium was seen in the proliferative phase in most, but not all, cases. Another change seen was that some of the fibrin of the clot in the wound appeared to be converted into collagen, which later became aerated in various ways. There was also re-expansion of many of the collapsed alveoli in the vicinity of the wound. Other alveoli were lined with cubical epithelium and resembled foetal lung tissue. These were probably newly formed, although the author does not exclude the possibility that they might have been re-expanded existing alveoli. The author was much impressed by the evidence in these sections of intense activity directed towards aeration of the scar tissue. The bronchial epithelium appeared to be affected by environment. When a bronchus was constricted or had to penetrate unusually dense collagen, it tended to become squamous in form. This

suggests the need for careful haemostasis in operations on the lung.

Oedema was absent in all wounds older than 45 hours. The amount of connective tissue diminishes with the increasing age of the wound. This may be due to the rich blood supply, which would not exist, for example, in a chronic tuberculous lesion.

The original paper contains much detail which cannot be discussed here. It is illustrated by 16 photomicrographs of sections of healing lung wounds at different stages.

Dusts causing Lung Disease

253

LUNG TUMOURS IN MICE AND MAN

by J. A. Campbell, *British Medical Journal*, 1, 179-183, 13/2/43

The author, who is a member of the scientific staff of the *National Institute for Medical Research*, London, summarises and reviews, with the aid of statistical methods, his results from more than ten years' experiments (1932 to 1942) with dusts. Mice in respiratory chambers were exposed once an hour, for six hours, on five days of each week for a year, to a moderate cloud of dust from various substances which have been under suspicion as causes of lung cancer in man. After the dusting was completed, the mice were not killed but were allowed to fulfil their allotted span of life. The author compares his findings with those elucidated from statistics of human lung cancer in Great Britain (Kennaway & Kennaway, 1936; Turner & Grace, 1938), and he refers also to the results of outstanding interest in other countries such as those reported for human lung cancer in Schneeberg (Rostocki, 1928; Schmorl, 1928) and in St. Joachimsthal, Czechoslovakia (Pirchan & Sikl, 1932). He compares these statistical data for human lung cancer with his data for mouse lung cancer as regards:

- a. Agents which increase the incidence of lung tumours;
- b. the time factor and the influences of age and sex;
- c. the factors of susceptibility and heredity;
- d. the morphology of the tumours.

Reference is also made to the influence of irritation, both chemical and mechanical.

The dusts tested by the present author on mice include those containing benzyrene from tarred roads, similar road dust with the tar removed by benzene, Czechoslovak dust containing some radium and arsenic, Czechoslovak dust without radium and arsenic, a nickel dust mixture containing arsenic which has increased the incidence of lung cancer in certain industrial workers in Great Britain, anthracite coal, bituminous coal, coal soot, exhaust soot from an internal combustion engine, steel grindings, silica, brown oxide of iron, alumina, and calcium carbonate.

The evidence of statistics for human lung cancer indicates that an abnormal liability to this disease has been observed among workers exposed to coal gas and tar, those engaged in the preparation and sale of tobacco, metal grinders, engineers, foundry workers, silica workers, chromate workers, workers with a nickel dust mixture, and Czechoslovak pitchblende miners. Also a rather high incidence has been observed in those whose occupation exposes them especially to road dust; these include paviours, road sweepers, and drivers of horse-drawn and motor vehicles. The inorganic substances, therefore, which appear to be dangerous to man include radium, arsenic, a nickel dust mixture, iron, and silica. With dusts containing these inorganic substances the incidences of lung tumours and lung cancer were definitely increased in the author's mice. The tarred road dust, with and without the tar, also increased the incidence of lung tumours in the mice, sometimes to a very high degree. In these respects, the results obtained in the dusting experiments with mice resemble those obtained from statistics for man.

With iron oxide the tumours produced in the mouse's lung were more numerous and malignant than those produced by silica. The author (Campbell, 1943) has recently pointed out that the silica dust did not produce silicotic nodules in the mouse's lungs, although the incidence of lung tumours was increased and there were silicotic nodules in the tracheo-

bronchial lymph nodes of about half the mice. He suggests that when silicotic nodules are produced in the lungs, cancer may be inhibited, and also points out that silicotic nodules may be regarded as simple multiple tumours.

With the aid of the microscope it was possible to distinguish between eight degrees of dust deposit in the lung tissue. When the dust deposit occupied about three-quarters of the lung tissue, it was arbitrarily termed a very heavy deposit, or 100% deposit. Half this amount or a moderate deposit was termed a 50% deposit. Most of the dust deposits which produced lung tumours in mice were only moderate or less in degree. From this the author concludes that the main effect of certain dusts in the development of lung cancer is a prolonged chemical irritation, but it is not possible to exclude entirely some effects of prolonged mechanical irritation by the harder or larger deposits of dust. Such large masses might produce a local stoppage of circulation with a resulting anoxia for the cells among the dust. The lymph tissue in the lung and tracheobronchial lymph nodes also contained deposits of dust which produced hypertrophy of the lymph tissue.

With regard to the influence of age, or the time factor, the large majority of deaths from human lung cancer occur after the age of 55 years—that is in the closing stages of life. Similarly in the mice experiments (Campbell, 1942) the tumours of the lung are rare until the last quarter of the average mouse life of two to three years. It is possible by means of intravenous injection of very small quantities of some of the new carcinogenic agents to produce lung tumours very early in certain strains of mice (Andervont & Shimkin, 1940). The author indicates that it is doubtful whether, with such rapid action, these results can be applied to the usual cases in which a prolonged action seems necessary, unless under these conditions inhibitory agents are present. Such inhibitory agents seem to occur in some mice whose lungs are very resistant to intravenous injection of powerful carcinogenic agents (Heston, 1942).

In human lung cancer males appear to be affected much more often than females, but some observers find that for simple adenoma the reverse is the case. Sex had no marked effect on the incidence of lung tumours in the mouse experiments (Campbell, 1942), but both the male and female mice were equally exposed to the dusts. In man, environmental conditions are usually different for the two sexes for a great part of the day and the author suggests that the entry of women into industry during the war may in time change the distribution of human lung cancer between the sexes.

The milk factor, recently discovered by Bittner (1942) of the U.S.A. to be so important for the development of mammary tumours in mice, has apparently no influence on the incidence of lung tumours. It is evident, however, that by close inbreeding (Strong, 1936) with brother-to-sister matings, it is possible to produce strains of mice either very susceptible or very resistant to development of lung tumours. In this respect, heredity is important, and in man there is a suspicion that some degree of inbreeding may have had an influence in the production of the high incidence of lung cancer in the Schneeberg and St. Joachimsthal miners, since there are similar mines in other parts of the world where there is no such high incidence of lung cancer. In the Czechoslovak region there are also cases of lung cancer among men who have never been in the mines. This seems to indicate some influence of heredity or some factors, for example iron and silica, present in the outside dust as well as in the mine dust. The factor which renders an individual susceptible to the dust is unknown.

Nucleoprotein is stated to be present both in the genes, which are concerned with heredity, and in certain viruses (Stanley & Knight, 1941). The author suggests that some link or chain in nucleoprotein may provide the bridge between the heredity theory and the so-called virus theory held by some observers for cancer in general. So far, there is no evidence that a virus is concerned in lung tumour development, unless a virus is similar to a gene.

In his dusting experiments, the author has produced mouse lung cancers which resemble closely human lung cancers in their morphology and the present paper contains photomicrographs of mouse lung cancers to illustrate this point. Almost all the types of cancer cells found in human lung cancer have been obtained in mouse lung cancers. These include the usual columnar cells of adenocarcinoma, spindle cells, large and small oat cells, spheroidal cells, round cells

and transitional cells between these types. Metastases composed of these various types of cells have also been obtained.

The author concludes from his experiments that there is a similarity between human lung cancers and mouse lung cancers as regards: (i) agents which increase the incidence of these tumours; (ii) the time or age factor; (iii) some aspects of the factor of susceptibility; (iv) morphology of the tumours. The dusts which were found most active in producing lung tumours in mice include tarred road dust with and without tar, Czechoslovak pitchblende dust, iron oxide, silica, and a nickel dust mixture containing arsenic, and the author considers that the main effect of these dusts is a prolonged chemical irritation. He also observed an hypertrophy of the lymph tissue in the lungs and in the tracheobronchial lymph nodes as a result of the exposure to the dusts. He states that there is no fundamental reason why the results obtained for lung tumours in the mouse experiments with dusts should not be applied to man.

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254

FAILURE OF ALUMINIUM TO PREVENT EXPERIMENTAL SILICOSIS

by T. Belt & E. J. King, *Journal of Pathology and Bacteriology*, 55, 69-73, January 1943

The research reported in this paper from the Department of Pathology of the *British Postgraduate Medical School*, London, is an attempt to confirm the important work of Denny, Robson & Irwin (1939) in which they found that experimental silicosis produced in rabbits by inhalation of powdered quartz could be prevented by admixture with aluminium powder, in the proportion of 1 part of the latter with 99 parts of quartz. The present authors used Kettle & Hilton's (1932) method of intratracheal insufflation instead of simple inhalation, and employed rats instead of rabbits. A single dose of dust was delivered into the lungs of each rat by means of a syringe inserted into the trachea. The dust was suspended in a fluid medium containing equal parts of saline and milk to emulsify the powdered aluminium. Each cubic centimetre of fluid contained 2 mg. of aluminium to 100 mg. of quartz and each rat received 1.5 cubic centimetres. The aluminium, however, failed to inhibit the development of silicotic nodules, although nearly all the nodules contained obvious collections of aluminium particles in their midst. Also in histological appearance there were no important differences from the nodules produced by the quartz alone. Chemical analysis of the lungs proved that the lungs contained aluminium and silica in a proportion higher than 1 in 100 which Denny and his colleagues found sufficient to inhibit the nodules. These observers maintain that this inhibition depends upon the formation of the hydroxide of aluminium and the present authors suggest that the failure of the aluminium to prevent silicosis in their experiments may be due to its being insufficiently hydroxylated. The reason for this is not known.

The authors also carried out some experiments in which 20 to 50 mg. of aluminium suspended in milk-saline were injected into the trachea without silica. They found that aluminium itself is capable of producing considerable pathological change. The metallic particles tend to collect in the terminal bronchioles, forming compact nodular masses which usually become incorporated in the bronchiolar mucosa, often bulging into the lumen, like a polypus, with bronchial

epithelium covering them. Relatively little of the aluminium dust gets past the terminal bronchioles into the air sacs.

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255

RADIOLOGICAL APPEARANCES IN THE DEVELOPMENT OF COAL MINERS' PNEUMOKONIOSIS

by E. A. Aslett, T. W. Davies, & T. I. Jenkins, *British Journal of Radiology*, 16, 308-313, October 1943

The radiographic appearance of the lesions of pneumokoniosis are well known, but the way in which they develop has not been studied so extensively. This paper is based upon the survey of 31 coal miners who were first x-rayed in 1938 during investigations¹ organised by the *Medical Research Council*, and were re-examined in 1942, 3½ years later. It was found that simple nodulation, seen in the earlier stages of the disease, developed into coalescent nodulation and finally into massive shadows. As well as these solid areas of fibrosis which produce massive shadows, a diffuse fibrosis develops in the advanced cases, which causes scarring and contraction and may be a factor in the production of generalised emphysema. In 4 cases the development of the disease was observed by tomography. This showed that the lesions were usually more extensive than they appeared on ordinary x-ray examination. The tomographs also suggested that, as the disease advances, the nodules are drawn together to form increasingly compact lesions which eventually become massive shadows.

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¹ *Medical Research Council, Special Report Series*, No. 244 (1943) H.M. Stationery Office, London

Diagnostic Microscopy in Pulmonary Tuberculosis and Carcinoma

256

CARCINOMA OF THE LUNG: The Value of Sputum Examination in Diagnosis

by F. J. S. Gower, *British Journal of Surgery*, 30, 193-200, January 1943

The author describes the results of examination of the sputum from 93 patients with suspected neoplasm of the lung, using the "wet-film" method described by Dudgeon (1936). The following is a brief description of the technique:

Fresh sputum, expectorated by the patient on waking in the morning, is collected and poured into a Petri dish. Blood-streaked portions or solid fragments are picked out for examination and smeared on slides. The procedure is then as follows:

- i. Fix, by immersing at once in a bath of Schaudinn's solution¹ for 20 minutes,
- ii. wash in 70% alcohol, containing a trace of iodine,
- iii. stain with Mayer's hæmalum² for 1½ to 2 minutes,
- iv. wash with tap water,
- v. counterstain with weak eosin,
- vi. dehydrate, and mount in Canada balsam.

The slides are examined systematically with a low-power objective, and any suspicious groups of cells are examined with greater magnification. The cells seen in normal sputum are squamous epithelial cells from the mouth and pharynx, and alveolar phagocytes (dust cells) from the lungs. In pathological conditions other types may be seen, such as

¹ *Schaudinn's solution*: Absolute alcohol, 1 vol. Saturated aqueous solution of mercuric chloride, 2 vols. To this stock solution, add glacial acetic acid to the strength of 3% immediately before use.

² *Mayer's hæmalum stain*: Hæmatoxylin, 1 gram. Distilled water 1,000 cm.³ Heat to dissolve and add sodium iodate 0.2 gram, ammonium aluminium sulphate 50 grams, glacial acetic acid 20 cm.³

pus cells, eosinophils, lymphocytes and swollen alveolar cells. Malignant cells occur in groups and stain more darkly than the other cells. Their nuclei vary in size and shape, and often contain nucleoli or mitotic figures. Considerable practice is necessary before malignant cells can be recognised with certainty, but with experience it is even possible to tell the type of carcinoma from which the cells originated.

Of the author's 93 cases, 65 had definite or probable primary growths of the lung; 36 of these had recognisable malignant cells in the sputum. In no case was a mistaken diagnosis made from sputum examination. Of the 36 patients whose sputum contained carcinoma cells, 13 had early growths and appeared operable, showing that the test is of value in the early diagnosis of carcinoma.

The author suggests that this test is a valuable addition to the methods of investigating cases of suspected bronchial neoplasm. It does not replace other diagnostic procedures, such as bronchoscopy but it has the same value as the examination of the sputum in pulmonary tuberculosis. A positive result proves the diagnosis, but a negative sputum test for carcinoma cells does not exclude the presence of a bronchial carcinoma.

This article also includes protocols of a number of typical cases, and some colour photomicrographs of carcinoma cells in sputum.

REFERENCE

Dudgeon, L. S. (1936) *St. Thomas's Hosp. Rep.* 1, 51

257

BACTERIOLOGICAL INVESTIGATIONS IN A MASS CHEST SURVEY

by J. W. Bigger, *Lancet*, 2, 699-700, 4/12/43

A preliminary miniature radiography survey of British Army personnel was carried out by Major P. Kerley in 1942, and full-size films were made of 5,737 radiologically abnormal cases. The present paper reports the findings in 20 of these cases referred for bacteriological investigations. The results of examination are set out in the table below:

Group	Diagnosis	Pa- tient's num- ber	Tubercle Bacilli		
			Sputum		Gas- tric juice (culture)
			micro- scopic	cult- ure	
I	Pulmonary infiltration considered to be non-tuberculous	1	—	0	0
		2	—	—	—
		3	—	—	—
		4	+	+	—
II	Healed pulmonary tuberculosis: no evidence of activity	5	—	—	—
		6	—	—	—
		7	—	—	—
		8	—	+	—
III	Radiological evidence of bilateral fibrosis and cavitation: no physical signs	9	—	—	+
		10	—	—	—
		11	—	+	+
		12	+	0	0
IV	Active pulmonary tuberculosis suspected	13	+	0	0
		14	+	0	0
		15	+	0	0
		16	+	0	0
V	Active pulmonary tuberculosis diagnosed	17	+	+	—
		18	+	+	+
		19	+	+	—
		20	—	—	+

+ = Tubercle bacilli found — = Tubercle bacilli not found
0 = Not examined

In all 10 cases diagnosed or suspected as active pulmonary tuberculosis, tubercle bacilli were demonstrated. The bacilli were also found in 3 other cases in which active pulmonary tuberculosis was not suspected on radiological or clinical grounds. The author concludes that culture of both sputum and fasting gastric juice is a practicable, valuable and early diagnostic method.

258

THE VALUE OF EXACT SPUTUM EXAMINATION (LARYNGEAL SWAB CULTURE) IN THE DIAGNOSIS AND MANAGEMENT OF PULMONARY TUBERCULOSIS

by D. Munro-Ashman & E. Nassau, *Tubercle*, 24, 79-84, May 1943

The authors refer to the difficulty of demonstrating tubercle bacilli in patients with minimal lesions. At the *Middlesex County Sanatorium*, Harefield, for the last three years, they have employed, in such cases, the technique of laryngeal swab culture as described by Nassau (1941). This technique is summarised, and its application is illustrated by eight case reports.

REFERENCE

Nassau, E. (1941) *Proc. roy. Soc. Med.* 34, 387

Neoplasm and Cystic Disease of the Lung

259

SURGICAL TREATMENT OF BRONCHIAL CARCINOMA

by R. C. Brock, *British Medical Journal*, 2, 257-259, 28/8/43

Primary carcinoma of the bronchus is a common condition in Britain at the present time, and ranks next to cancer of the colon in frequency in men. Although deep x-ray therapy may produce a temporary improvement, surgery is the only form of treatment which can achieve a cure. Early diagnosis is essential if surgery is to be successful, and the slightest symptoms in a middle-aged man should be regarded with suspicion and thoroughly investigated.

The commonest early symptom of a bronchial carcinoma is cough; later bronchial obstruction occurs and this is followed by infection of the lung. Recurrent pulmonary sepsis, or the delayed resolution of a pneumonia, in a middle-aged patient should rouse the suspicion of malignant disease. Necessary investigations include good antero-posterior and lateral radiographs of the chest, bronchoscopy and sometimes bronchography.

Four questions are commonly asked about the operation of pneumonectomy for bronchial carcinoma, and Brock gives answers to these questions based upon his own experience:

i. *How often is it possible to operate?* In a total of about 450 cases, seen over a period of 9 years, the chest was explored in 65, and of these 29 were found to be operable. Thus, at the present time, less than 10% of the cases diagnosed are operable, a fact which clearly shows the importance of early diagnosis.

ii. *What is the mortality?* Of the 29 operable cases (26 pneumonectomies and 3 lobectomies), 8 died from the operation, 7 died from recurrence of the growth, and 14 are alive and well. Many of these patients were in poor condition and this number also includes some who underwent the operation as long as 4½ years ago. Recently there have been numerous improvements in technique which are reducing the mortality. In another series of 10 pneumonectomies and 4 lobectomies for bronchial adenoma, there were only 2 deaths. Brock concludes that the mortality from pneumonectomy for carcinoma in a patient under the age of 60 and in good condition, should not much exceed 10%.

iii. *How long may the patient be expected to survive?* In Brock's series, 7 of the 21 survivors died of recurrence; 5 of them within a year of operation. The prognosis is better when the growth is of the squamous-celled type.

iv. *How much can the patient do after a successful pneumonectomy?* Disability is negligible or absent in almost all cases. Occasionally there may be a discharging sinus but this only occurred in one of Brock's 21 cases. There is no deformity, and the patient is able to return to his previous occupation.

260

THE EARLY DIAGNOSIS OF NEW GROWTHS OF THE LUNG

by W. D. W. Brooks, *Practitioner*, 150, 75-81, February 1943

For purposes of discussion the author defines "early" diagnosis of pulmonary neoplasms as their diagnosis before metastasis or local complications have occurred. He discusses the apparent rise in incidence of pulmonary neoplasms, stresses the need for effective treatment, and believes that present diagnostic measures do not permit of identification at an early enough stage. New diagnostic measures are a necessity. In benign lung tumours early surgical intervention is simple and fairly safe, with good prognosis. Of benign bronchial tumours, adenomata are the most common; the histological examination of material removed at bronchoscopy is the most important means of diagnosis. In bronchial carcinomata the examination of sputum by the wet film method of Dudgeon is an important diagnostic procedure, while bronchoscopic examination reveals nearly 80 % of such growths.

261

CYSTIC DISEASE OF THE LUNG (BRONCHO-ALVEOLAR CYSTS)

by F. E. S. Willis & J. Almeyda, *Tubercle*, 24, 27-36 & 43-58, February & March 1943

The authors, from the *Royal Chest Hospital*, London, use the term "broncho-alveolar cysts" to include all varieties of lung cysts, both congenital and acquired, with the exception of mediastinal and pleural cysts, parasitic cysts and those arising from the breakdown of lung tissue. Calma (1941) pointed out that pulmonary cysts could be either bronchial or alveolar in origin and the authors suggest the following classification of cysts of the lung based on this division:

- a. *Alveolar Cysts* (containing air)
 - i. Pneumatocele or solitary alveolar cyst
 - ii. Cystic emphysema or multiple alveolar cysts
- b. *Bronchial Cysts* (containing air, fluid or both)
 - i. Pneumocyst or solitary bronchial cyst
 - ii. Cystic bronchiectasis or multiple bronchial cysts.

In distinguishing between acquired and congenital cysts, the absence of pigmentation and the absence of pleural adhesions and other inflammatory changes suggest a congenital origin. Both bronchial and alveolar cysts tend to communicate with the bronchi and if these communications become partially obstructed, the cyst may become distended with air. Alveolar cysts have a thin wall which is lined with flattened epithelium and contains little muscular or elastic tissue. Bronchial cysts have smooth muscle, elastic tissue and sometimes cartilage in their walls and they are lined with columnar, ciliated epithelium.

In a series of 85 patients considered to have cystic disease of the lung the authors found 60 of the bronchial type and 25 of the alveolar type. The clinical picture depended on the extent of the disease and the occurrence of complications such as infection or tension within the cysts. Haemoptysis was uncommon with alveolar but common with bronchial cysts. In only one case was there any evidence of a familial tendency to the disease. Complications were present in the majority of instances; spontaneous pneumothorax was the most common complication of the multiple alveolar type of cystic disease, while infection and its sequelae, such as pneumonia and lung abscess, were the most frequent complications of bronchial cysts.

It may be impossible to distinguish radiologically between the solitary bronchial cyst and the solitary alveolar cyst. The former is usually the smaller and tends to have a thicker wall but, in both, the remainder of the bronchial tree may be normal, apart from distortion, and both may have bronchial communications. Multiple alveolar cysts have a typical

"soap bubble" appearance on the x-ray film. Multiple bronchial cysts are of two types; in one the affected area is a mass of irregular cystic spaces like a sponge, in the other there are multiple spherical dilatations of the bronchi.

The authors do not discuss the treatment, but express the hope that a fuller understanding of the clinical and pathological features may help in deciding upon a suitable therapy in individual cases. The original paper contains 21 illustrations (1 diagram, 4 photographs, 2 photomicrographs, and 14 radiographs).

REFERENCE

Calma, I. (1941) *Brit. J. Tuberc.* 35, 40

Therapeutic and Traumatic Collapse of the Lung

262

EFFECT OF ALTITUDE ON CASES OF PNEUMOTHORAX

by G. S. Todd & D. M. Anderson, *Lancet*, 2, 597-600, 13/11/43

This investigation was undertaken in order to ascertain the effect of flying upon patients with a pneumothorax. This is an important matter in wartime when it may be necessary to transport cases of traumatic pneumothorax by air. Five patients, each with an artificial pneumothorax, were investigated in a special chamber in which the pressure could be adjusted to represent the atmospheric conditions at various altitudes. In this chamber there were facilities for radiological and electrocardiographic examination, and for estimating the vital capacity and collecting samples of the alveolar air.

As the pressure was reduced, the air within the pneumothorax expanded, the lung was compressed and the mediastinum, if mobile, was displaced to the opposite side. The vital capacity was reduced and, at a certain pressure varying with the individual but corresponding with an altitude of between 4,000 and 8,000 feet [about 1,220 to 2,440 m.], the patient began to complain of dyspnoea and distress. Patients with a mobile mediastinum appeared to tolerate high altitudes better than those with a fixed mediastinum. The partial pressures of oxygen and carbon dioxide in the alveolar air showed a progressive fall, but the symptoms were due to the mechanical effect of tension rather than to oxygen lack. The electrocardiographic changes were negligible even when there was marked lateral displacement of the heart.

The authors conclude that no patient with a pneumothorax should be transported by air at a height greater than 4,000 feet. Patients with tension-pneumothorax should not be carried by air at all unless a needle or intercostal catheter has previously been inserted into the pleural cavity and a doctor is in attendance to adjust the pressures during the flight. Pilots or passengers with an artificial pneumothorax should not fly above 4,000 feet for any length of time and should on no account go above 8,000 feet.

The paper is illustrated by serial radiographs taken at different atmospheric pressures and by diagrams of the screen appearances.

263

SOME OBSERVATIONS ON EIGHTY CONSECUTIVE CASES OF INTERNAL PNEUMONOLYSIS

by R. S. Barclay, *Edinburgh Medical Journal*, 50, 554-557, September 1943

This short paper is based on a series of 80 patients undergoing artificial pneumothorax treatment in whom thoracoscopy with section of adhesions was performed at *Ruchill Hospital*, Glasgow.

The total number of thoracoscopies was 103, as some patients required more than one intervention.

In 57 patients there was an obvious cavity, closure of which was prevented by adhesions. In the remaining 23 patients, adhesions were preventing concentric collapse of the lung.

The author classifies his results as :

Group A (62.5 %) : Complete division of adhesions and control of the disease.

Group B (10 %) : Incomplete division of adhesions, but control of the disease.

Group C (15 %) : Incomplete division of adhesions and disease not controlled.

Group D (12.5 %) : Impossible to cut adhesions because of fusion of lung with chest wall.

There were no deaths in the series, and patients were little disturbed by the operative procedures.

The author points out that over 70 % of unsatisfactory types of pneumothorax were converted to satisfactory types by this treatment.

264

PNEUMOPERITONEUM IN THE COLLAPSE THERAPY OF PULMONARY TUBERCULOSIS

by E. Clifford-Jones & N. MacDonald, *Tubercle*, 24, 97-107, June 1943

The authors, who write from the *Middlesex County Sanatorium*, South Mimms, claim that pneumoperitoneum is a useful adjunct to other forms of collapse therapy. They have had experience of over 60 cases so treated and observed for periods of 3-15 months. Ten of these cases are described in detail in the present paper. The rationale of the method, the indications for its use, and the sequelæ and complications are discussed. A full description of the technique is given. The paper is illustrated by reproductions of 16 radiographs. The authors express their intention of publishing at a later date a fuller report based on a larger series of cases.

Surgical Treatment of Pulmonary Tuberculosis

In the modern treatment of pulmonary tuberculosis, more and more stress is being laid upon the necessity of closing tuberculous cavities. When collapse therapy is indicated, it must be based on sound mechanical principles and it must aim at cavity closure. For this reason the following three papers [BMB 265, 266, 267] are of particular interest. In them C. Price Thomas (Assistant Surgeon to the Brompton Hospital, London) discusses the mechanism by which cavities in the lung may become closed and gives a detailed description of the technique and results of the modern thoracoplasty operation.

265

PULMONARY CAVITIES : Their Persistence and Closure
by C. Price Thomas, *British Journal of Tuberculosis*, 36, 4-19, January 1942

It has long been recognised that the healing of a pulmonary cavity is accompanied by obliterative changes in the bronchi which drain it. The author suggests that a very early cavity, produced by the rupture of a tuberculous focus into a bronchus, will tend to close spontaneously as a result of the inherent retractility of the lung, provided that there is free bronchial drainage and sufficient healthy lung around the cavity to allow compensatory emphysema to occur.

Persistence of such a cavity may be due either to continued ulceration of the lung, to the traction of the chest wall, or to the inflationary action of the bronchial air stream; the last factor is probably the most important. It is suggested that the tuberculous process causes a partial stenosis of the draining bronchus, so that air is trapped in the cavity and prevents it from closing. As the disease progresses, free bronchial drainage often becomes established, but by this time the affected area is usually adherent to the chest wall and this holds the cavity open. Even at this stage, however, complete occlusion of the draining bronchi will cause obliteration of the cavity by absorption of the air within it, if the lung can be relaxed. Therapeutic measures such as rest, artificial pneumothorax, diaphragmatic paralysis and thoracoplasty, cause tuberculous cavities to close by promoting obliteration of their draining bronchi. This takes

place by diminution of the inspiratory traction on the bronchial walls and, in the case of relaxation methods, by reducing the calibre of the bronchi and thus converting a partial into a complete stenosis.

266

EXTRAFASCIAL APICOLYSIS WITH THORACOPLASTY

by C. Price Thomas & W. P. Cleland, *British Journal of Tuberculosis*, 36, 109-138, July 1942

The most perfect form of pulmonary collapse is that produced by an artificial pneumothorax completely free from adhesions. This gives concentric relaxation of the lung, which in turn relaxes the cavity and its draining bronchi and eliminates inspiratory traction on the diseased area.

The ordinary paravertebral or lateral thoracoplasty will close the cavity in only about one-third of cases, because it does not allow vertical relaxation of the lung. In fact, when operating again upon a patient who has had a paravertebral thoracoplasty, the forcible movement of the apex of the lung with each inspiration may readily be seen.

The combination of apicolysis with thoracoplasty overcomes this disadvantage and reproduces, as closely as possible, the conditions of concentric relaxation obtained by artificial pneumothorax. The apex of the lung should be mobilised in the extrafascial plane, rather than in the extrapleural plane, because it is then less liable to re-expand, there is less danger of opening tuberculous cavities, and the procedure can be applied to all types of case. Semb, who first described this operation, advocated the removal of the first 3 ribs only at the first stage. Price Thomas adds to this, resection of limited segments of the posterior ends of the 4th and 5th ribs.

This new technique allows extensive stripping of the apex on the mediastinal surface and in the paravertebral gutter, but leaves a stable chest wall below the level of the 3rd rib, thus preventing paradoxical movement. The cavity and its drainage area can often be completely relaxed at the first operation, and over 90 % of cavities can be closed by this method in selected cases. Further resections of rib are carried out at later operations until relaxation has been extended downwards to include the 7th rib, so that the scapula can be properly bedded in front of the 8th rib.

In the selection of cases for operation, the patients may be classified into three groups, (i) stationary, (ii) relapsing, and (iii) "slipping," according to the way in which their disease is progressing. Those in the first two groups are the most suitable for thoracoplasty. The relapsing case should be treated during a period of clinical improvement. Patients in the third group, who are slowly but progressively deteriorating, are occasionally suitable for operation; for example, those with only a little, stationary disease in the relatively healthy lung, and in whom deterioration is slow; but such cases require very careful selection.

The age of the patient must also be considered. Operation is rarely indicated over the age of 45. The age of the disease is also important. If it is of 8 to 10 years' duration, the prolonged toxæmia will often have impaired the patient's capacity to withstand operation.

Pre-operative treatment includes careful tuition in diaphragmatic breathing and instruction in arm and shoulder movements. Patients are also made to practise wearing an oxygen mask, and are taught to cough gently but effectively.

Local anaesthesia is used for the operation, and includes blocking the brachial plexus and the intercostal nerves in the intervertebral foramina. The advantages of local anaesthesia are :

- i. Quiet respiration, which reduces the paradoxical movement of the mobilised apex,
- ii. preservation of the cough reflex, enabling the patient to keep his bronchial tree clear during the operation,
- iii. reduction of hæmorrhage by the use of adrenaline mixed with the local anaesthetic,
- iv. reduction of post-operative shock.

At the first-stage operation, the 3rd rib is resected subperiosteally, followed by the 2nd and then the 1st. The apex is then mobilised in the extrafascial plane. The extent of the mobilisation is determined by the type of disease and the condition of the patient; a soft apex and a toxic patient

are indications for restricted mobilisation, but in the case of a firm solid apex it is safe to resect the posterior parts of the 4th and 5th ribs and to continue the separation down to this level.

The second-stage operation is carried out 14 days after the first, if the patient's condition is satisfactory. It consists of further rib resections to carry the relaxation below the level of the diseased area. Patients who are in poor condition require small rib resections with mobilisation at each stage.

The most important accident which may occur during operation is the opening of a tuberculous pulmonary cavity. When this happens, the cavity should be aspirated, and mobilisation should be continued down to the 7th rib, thus freeing the cavity completely. It should then be closed firmly with three layers of catgut sutures.

After operation, the patient is nursed in the semi-recumbent position, and oxygen is used freely when necessary. Expectoration of sputum is encouraged by the administration of expectorants, with small doses of morphia to allay the pain of coughing, and by firm manual pressure to support the mobile chest wall while coughing. Blood transfusion is occasionally required between the stages of the operation.

Gentle arm and shoulder movements and breathing exercises are started on the 2nd or 3rd day after operation, in order to reduce scoliosis and to preserve the mobility of the arm. These exercises reduce the final deformity to a minimum. After the last stage, the patients are kept in bed for 12 weeks to allow firm healing of the cavity, and later they are given graded exercise at a sanatorium.

Post-operative complications include:

i. *Atelectasis*. This is seen in about 20 % of cases; it is due to bronchial obstruction from retained sputum and occurs commonly on the 2nd or 3rd day after operation. The physical signs and x-ray reveal displacement of the mediastinum to the affected side, with collapse of the lung. This is most common on the side of the operation. Treatment consists of encouraging expectoration, as already described, combined with postural drainage. In most instances the lung gradually re-expands but, in a few, pulmonary suppuration or tuberculous spread occurs. Such patients, if they survive, require a total thoracoplasty to relax the whole lung.

ii. *Spread of tuberculosis*. This may delay the operations but will usually resolve sufficiently to enable them to be completed.

iii. *Pneumonia due to other organisms*. This is not common and it will sometimes respond to sulphonamide therapy.

iv. *Spontaneous pneumothorax*. This may occur on either side.

v. *Infection of the extrafascial space*. This is manifested by persistent pyrexia, and distention of the space can be seen in the radiograph. If, as is most common, the infection is tuberculous, the space must be aspirated, but if it is pyogenic the space must be drained with a tube.

vi. *Hæmorrhage into the extrafascial space*. This is treated by aspiration and blood transfusion if required.

[A very full account of the operative technique, including details of the local anaesthesia and many illustrations, is given in the original article.]

267

THE RESULTS OF THORACOPLASTY

by C. Price Thomas & W. P. Cleland, *British Journal of Tuberculosis*, 37, 2-9, January 1943

In this paper the authors review 120 cases treated by thoracoplasty in a period of 7 years. The duration of observation after operation varied from 1 to 9 years, and there was a steady decrease in the operative mortality during the period under review, as increased experience was gained in selecting cases for operation and in technique. The more extensive modern thoracoplasty with apicolysis actually carries a much lower mortality than the earlier lateral thoracoplasty.

Employing the classification of disease already described,¹ it is shown that the mortality in the "slipping" case is six times as great as in the "stationary" case. It is interesting

that patients in whom the disease had been present for more than 2 years fared much worse than those with earlier disease; this suggests that the operation should not be delayed too long in the hope that fibrosis will occur, for the longer the disease is present, the more extensive will it become.

There is a direct relationship between the extent of the disease in either lung and the operative mortality. In a group of 30 patients with less than two-thirds of one lung affected, and minimal or no disease in the opposite lung, there were no deaths; whereas in a similar group of 28 patients with moderate disease in the contralateral lung there were 8 deaths. In a series of 23 patients with total involvement of one lung and moderate disease of the other, 13 died. A pneumothorax is often of value in controlling disease in the contralateral lung before operation.

The authors' operation, embodying an extensive apicolysis, is more effective than any other in promoting cavity closure. In fact, there was no failure to close the cavity in a series of 25 cases, whereas out of 72 patients treated by thoracoplasty with apicolysis down to the 4th rib only (Semb's operation), 41 still had open cavities. The great importance of cavity closure is clearly shown by the survival rates. Of 51 patients whose cavities closed after operation only 1 died, and in 3 the cavity re-opened. Of 45 patients who still had open cavities after operation, 11 died.

The figures also show clearly that the operation of thoracoplasty does not itself cause permanent incapacity, for in a series of 58 patients, 45 were working, in most cases at their previous occupation. The authors conclude that the more extensive thoracoplasty operations employing apicolysis increase the prospects of cavity closure and sputum conversion, but they do not increase the mortality or the risk of complications.

268

CLOSED SUCTION DRAINAGE OF TUBERCULOUS CAVITIES

by T. H. Sellors, *Tubercle*, 23, 239-250, November 1942

Until recent years the drainage of tuberculous cavities was rarely performed because of the fear of disseminating the disease by opening healthy lung tissue. Coryllos, Monaldi and others have now shown that closed suction drainage can be used successfully in the treatment of certain types of tuberculous cavity, and this method has been the subject of much recent clinical research in Great Britain. The present author reviews the results of this type of treatment in the light of his own experience of over 100 cases. He suggests that suction drainage should be applied only to the large, thin-walled, spherical type of cavity. Such a cavity is kept open because valvular stenoses of the bronchi which communicate with it allow air to enter but not to escape from the cavity; it is surrounded by a zone of compressed lung tissue which will re-expand and allow the cavity to close when the pressure of air within it is reduced. The ideal case for drainage is that in which the patient has a cavity of this type with little surrounding infiltration, and in which a pneumothorax has failed. Cases with multiple or thick-walled cavities and heavy pulmonary infiltration are not suitable for this form of treatment. The author stresses that suction drainage by itself will rarely produce permanent closure of a cavity and that it is most useful as a preliminary to some other form of mechanical collapse therapy, particularly thoracoplasty.

In his description of the technique of drainage the author emphasises the importance of ensuring that the pleural layers are adherent over the selected site. If a large pneumothorax pocket can be induced, the insertion of a thoracoscope and powdering the lung surface with 0.5 % iodine in talc powder is the best method of producing adhesions. In the case of a small pocket the injection of 0.1 to 0.3 cm³ of 10 % silver nitrate solution [see also *BMB* 44] or 0.05 g. of sodium aurothiosulphate ("crysalyne," "sanocrysin") in 2 cm³ of saline solution has been found to be effective. When the pleura is adherent, the cavity is localised carefully by means of x-rays and fluorography, and a fine barium-impregnated rubber catheter is inserted into it with a special trocar and cannula. This operation is not performed under the x-ray screen because of the danger to the operator's hands. In treating an apical cavity the tube is usually inserted through the first or second intercostal space anteriorly.

¹ [*BMB* 266]

Continuous suction is applied to the tube by an electric pump, and the author advocates a negative pressure of 3 to 5 cm. of mercury [compare *BMB* 269]. Progress is controlled by serial radiograms, and the tube is shortened as the cavity becomes smaller. The patient usually feels immediate benefit from the treatment because the amount of his sputum is reduced.

The results of cavity drainage in 82 cases are analysed: the size of the cavity was reduced in 49 instances, in 14 there was no appreciable change, in 12 the cavity appeared to be obliterated, and in 7 it closed but reappeared. A thoracoplasty was subsequently performed in 21 cases, but in most of these a less extensive operation was necessary than would have been the case if the cavity had not been drained. When performing an upper thoracoplasty after draining an apical cavity, the extent of the apicolysis may have to be limited to avoid encroaching on the track of the drainage tube.

The author believes that the possible indications for cavity drainage will increase if it is understood that it is only a preliminary procedure and not a final form of treatment.

269

THE DRAINAGE OF TUBERCULOUS CAVITIES

by R. J. C. Maxwell & M. L. Kohnstamm, *British Journal of Tuberculosis*, 37, 24-43, January 1943

The authors, from the Surrey County Sanatorium, give a very full account of the technique and indications for the drainage of tuberculous cavities. Their apparatus for applying suction consists of a pump with a regulating device designed to give a very gentle negative pressure. After a cavity has been drained, a suction of -2 to -4 cm. of water is applied during the day and discontinued at night; this is increased very gradually over a few weeks until a maximum suction of -15 cm. of water is reached. Higher negative pressures are said to rupture the fragile capillaries in the cavity wall. These authors have studied the fistulæ by which cavities communicate with the bronchial tree by means of x-rays taken after iodised oil has been inserted into the cavity through the drainage tube. They consider that cavities which have more than four bronchial fistulæ will not respond to drainage, but that those with three fistulæ or less will be reduced in size and very occasionally may become permanently closed. They regard suction drainage as a preliminary to surgical collapse rather than as a curative procedure, and they stress its value in improving the general condition of the patient and lessening the extent of the subsequent thoracoplasty.

270

ARTIFICIAL BRONCHIAL OCCLUSION BY PLASMA CLOT IN THE TREATMENT OF CHRONIC TUBERCULOUS CAVITATION

by D. Thomas, J. Gough & B. M. Still, *British Journal of Tuberculosis*, 37, 44-46, January 1943

The authors, from Sulley Hospital and the Welsh National School of Medicine, working on the theory that occlusion of the bronchi communicating with a tuberculous cavity will allow the cavity to close, have evolved a means of plugging these bronchi. A Monaldi drainage tube is first inserted into the cavity and, theoretically, if the bronchial fistulæ are then closed, suction on the tube will cause the cavity to become obliterated. Twenty cm.³ of blood are taken from the patient into a sterile tube in which 2 cm.³ of a 1.35% solution of sodium oxalate have been evaporated to dryness. The oxalated blood is then centrifuged and the plasma is removed. One cm.³ of the plasma is mixed in a test tube of 1 cm. diameter with 0.2 cm.³ of diodone [a mixture or loose combination of 3, 5-diiodo-4-pyridone-N-acetic acid and diethanolamine, known also as "Per-Abrodil" and "Pyelosil"] and 0.8 cm.³ of viper venom (Stypven). 0.1 cm.³ of a 4.5% solution of anhydrous calcium chloride is then added, and the clotting time is measured with a stop watch. This should be from one to three minutes at room temperature. Sufficient plasma to fill the cavity and its draining bronchi is then taken and mixed with the appropriate amounts of diodone and viper venom; finally the calcium chloride is added and the mixture is injected through the drainage tube into the cavity, during the last thirty seconds before it is due to clot. The authors claim that, if the injection is successful and the

patient does not cough, firm plugs of fibrin form in the bronchi and occlude them. This work is still only in a preliminary stage but the results are promising.

Chest Surgery in Wartime

271

WAR WOUNDS AND INJURIES OF THE CHEST

by A. Tudor Edwards, *British Journal of Surgery*, 31, 74-86, July 1943

This is a critical review by one of the most distinguished of contemporary thoracic surgeons and contains 89 references to the literature.

The author discusses the incidence of wounds of the chest in previous wars and points to the relative increase in the number of chest casualties under modern battle conditions. In the section on non-penetrating injuries are discussed simple fractures of one or more ribs; anterior and posterior fractures of several ribs resulting in partial collapse and paradoxical movement of a segment of the chest wall; traumatic asphyxia; injuries of the lung and pleura; cardiac injuries; and injuries from explosion blast. In the section on penetrating wounds, tension pneumothorax, open pneumothorax, and indications for early operation are included.

There are separate sections on abdomino-thoracic wounds, hæmorthorax,¹ late removal of foreign bodies, atelectasis in chest injuries, the value of radiology, wounds of heart and pericardium, diaphragmatic hernia, and transport. The use of sulphonamides in the prophylaxis and treatment of infection receives attention in different sections.

¹ [see *BMB* 45 for a review of a paper by the same author on traumatic hæmorthorax.]

272

THORACIC INJURIES: The Rôle of the General Surgeon in the Forward Area

by C. Price Thomas, *British Journal of Tuberculosis*, 37, 103-115, July-October 1943

War experience in Libya has shown that the specialised thoracic surgery unit should be mainly concerned with the later treatment of chest injuries in relatively stationary areas.

The more serious thoracic injuries often cause death by interference with the cardio-respiratory system before there is any possibility of removal to an operating unit. After the first 48 hours, infection is the commonest cause of death.

The forward (non-specialist) operating unit should aim at reducing shock, by the use of warmth, morphine, transfusion and oxygen. Radiographs should be taken when an x-ray unit is available. The commonest causes of interference with the cardio-respiratory system are (i) open pneumothorax and (ii) tension pneumothorax. The author outlines the emergency treatment of both these conditions.

Surgical emphysema is only occasionally severe. When present it should be treated by finding and dealing with its cause—often a tension pneumothorax. The older method of multiple incisions is discredited.

Severe crushing of the chest wall, with paradoxical movements, requires strapping, reinforced by cardboard or plaster of Paris. Hæmopericardium is not common, and it is doubtful whether surgical intervention should be attempted by the forward operating unit. Hæmorthorax, except (i) where ribs are shattered on the entry side, (ii) in the case of parasternal wounds, should be treated conservatively by aspiration without gas replacement.

The author concludes with a warning against too great a reliance on chemotherapy. Scrupulous surgical technique remains essential.

273

THE PATHOLOGY OF CLOSED INJURIES OF THE CHEST

by J. V. Wilson, *British Medical Journal*, 1, 470-474, 17/4/43

The conclusions of the author, who is serving with the British Army, are based on two years' experience of performing routine autopsy examinations on battle casualties.

By a closed injury is meant one in which the pleura has not been penetrated; such injuries may be grouped under the following headings:

i. *Lacerations.* Rupture of the heart or great vessels usually causes instant death. Laceration of the lung is common, rarely severe, and seldom causes death by itself but its complications may be fatal. The chief of these are hæmorrhage, compression of the lung and infection. Hæmopneumothorax is common and requires prompt treatment, the amount of air in the pleural cavity is usually not great, but bleeding is often profuse. Hæmorrhage from the lung is rarely severe, as the pressure in the pulmonary artery is low, but bleeding from intercostal or the internal mammary vessels is often profuse and difficult to control. In addition, the blood acts as a foreign body and causes an outpouring of exudate from the pleura, which increases the volume of the effusion and the dehydration of the patient. Blood in the pleural cavity often remains fluid; this may be due to the absence of thrombokinas in cases where there is little tissue damage, or to defibrination of the blood by the movement of the lung and heart. Compression of the lung by air, fluid, or both, is another common complication. Infection of the pleural contents from the lung can occur in closed injuries.

ii. *Contusions.* Bruising of the thoracic viscera is most often seen in young subjects in whom the chest wall is elastic. Myocardial contusions may be caused by a direct blow on the chest or by high explosive blast. The anterior surface of the ventricles is the most common site and the myocardium appears dark and hæmorrhagic, not unlike an infarct. Rupture of the heart may occur. Pulmonary contusion due to direct trauma produces an area of hæmorrhage at the site of the blow and generalised congestion with small scattered capillary hæmorrhages throughout the lung. The lesions are identical with those observed following exposure to blast.

iii. *Blast injuries.* The common findings are scattered areas of hæmorrhage throughout the lungs, both subpleural and deep in the parenchyma, dark subpleural hæmorrhages along the lines of the intercostal spaces, and often extensive hæmorrhages posteriorly in the region of the apex and those parts of the lung in contact with the paravertebral structures. If the injuries are not immediately fatal, recovery is the rule, the hæmorrhages coagulate and absorb like a pneumonic exudate. The chief complications are pneumothorax, acute pulmonary oedema with heart failure, and bronchopneumonia. The lesions are probably due to the impact of the pressure wave on the chest wall and are therefore similar to contusions. Many cases also show bruising of the myocardium and mediastinal structures. The cause of death in blast injuries is still uncertain; it may be due to the pulmonary hæmorrhages, to cerebral damage from compression, to ventricular fibrillation following contusion of the heart, or to air embolism.

[see also BMB 274]

274

PATHOLOGICAL FINDINGS IN A SERIES OF BLAST INJURIES

by J. V. Wilson & R. E. Tunbridge, *Lancet*, 1, 257-261, 27/2/43

A number of pathological studies on blast injuries have already been published. The present series is reported because of the uniqueness of the incident, the large number of cases involved, and the strong evidence that blast alone was the cause of death.

During a heavy dive-bombing attack at Malta, a bomb fell in front of, and within five yards from, the entrance of a deep and crowded tunnel shelter in solid rock, open at both ends and entered by three right-angled turns. The flame passed straight into the entrance, blackening the rock, and survivors described a wind of tremendous force sweeping through the shelter. The electric light was extinguished and the inmates were thrown against each other. The bomb was probably of 500 kg. size. The entrance was completely demolished, but the shelter itself was intact; the concrete roof of the exit was disturbed. Many of the occupants were sleeping in cubicles hewn in the rock at the sides of the shelter at the time of the explosion. Those standing in the entrance were dismembered.

Help arrived within five minutes of the explosion. The first person to enter the shelter after the incident, thought at first that all the occupants were dead, as no one moved or answered. However, this was not so, and though all survivors were confused and dazed some were later able to return home without medical treatment. There was no evidence of burning or noxious fumes. A number of persons in bunks near the entrance were dead. Amongst the fatalities (eleven immediate and one eight hours later) were twelve in which no external injuries were seen and death could be presumed to be purely an effect of blast. Postmortem examinations (excluding the brain and spinal cord) were made upon these and are described in detail in the original paper. The finding which was characteristic of all these cases was the presence of extensive bilateral pulmonary hæmorrhages, associated with frothy blood-stained fluid in the mouth and upper air passages. The pulmonary hæmorrhages involved the deeper portions of lung tissue, and were continuous with gross ecchymoses on the surface of the lungs and visible beneath the pleura. These subpleural hæmorrhages had no constant pattern and varied considerably in extent. Rib markings were a feature of all cases. The sites of election for the sub-pleural hæmorrhages were the anterior margin, the costal surface, and the posterior surface of the lungs: the inferior margin was never extensively involved. Microscopically, there was hæmorrhage into the alveoli and marked congestion of the alveolar capillaries, even in areas free from gross hæmorrhage and, it is interesting to note, in a few cases there was oedema-fluid in the alveoli.

In the abdomen, in six cases, the vessels of the omentum, mesentery and peritoneum were congested and surrounded by small ecchymotic hæmorrhages. There were no ruptures of abdominal viscera. In one case there was a rupture of the aorta.

In their discussion of the cause of death the authors exclude poisoning by gaseous fumes or carbon monoxide, asphyxia, burns, fat embolism, and trauma other than that due to blast: they conclude that the primary lethal factor was blast. They concur with the view of Zuckerman (1940) that the lesions are produced by the traumatic effect of the blast upon the chest wall. They consider that the pulmonary lesions are not always of themselves sufficient to cause death and that, in such instances, the cause may lie in an acute effect upon certain vital centres.

REFERENCE

Zuckerman, S. (1940) *Lancet*, 2, 219

[see BMB 46 for a short list of papers dealing with the effects of explosion blast on the lungs; also BMB 273 in this number.]

Scope of Chest Surgery: Rehabilitation: Chest Radiography: Atypical Pneumonia

275

THE SCOPE OF MODERN CHEST SURGERY

by O. S. Tubbs, *Practitioner*, 150, 82-88, February 1943

The author reviews the part of the surgeon in the treatment of acute empyema, chronic non-tuberculous empyema, lung abscess, bronchiectasis, bronchial tumours, chest injuries, suppurative pericarditis, patent ductus arteriosus, and angina pectoris. Surgical methods and post-operative care are referred to only in connection with diseases likely to be treated in small hospitals. The surgical treatment of pulmonary tuberculosis is excluded, as tuberculous patients are not usually referred to the surgeon by the general practitioner, to whom this paper is chiefly addressed.

276

REHABILITATION OF THE CHEST CASE

by F. R. Edwards, *Lancet*, 1, 81-84, 15/1/44

In this paper from the Liverpool and North Western Unit of the *Emergency Medical Service* the author defines the special measures necessary for the restoration to optimal functional capacity of a patient who has sustained a chest injury or operation. Rehabilitation of the chest case is

based on the same fundamental principles as other forms of rehabilitation, but differs in detail.

Nearly all patients who enter a thoracic rehabilitation centre complain of dyspnoea on exertion. This is associated with a reduction in vital capacity attributable to (i) weak respiratory musculature from trauma and long rest in bed, (ii) damage or distortion of ribs, (iii) pleural thickening and adhesions, (iv) pulmonary fibrosis after destructive inflammatory lesions, (v) loss of lung tissue, as in lobectomy or pneumonectomy, (vi) emphysema, which is commonly found in military patients and often attributable to the unnaturally erect stance adopted, (vii) pain after fracture of ribs, operation, or insertion of drainage tubes.

These factors leading to diminution in vital capacity may be present singly or in association. They should be separately assessed and the appropriate remedial measures should be taken.

The investigation of the patient on admission to the rehabilitation centre includes a full history; clinical and radiographical examination; measurement of weight, chest expansion, and abdominal expansion. A spirographic tracing is taken, and gives information on tidal air; pulmonary ventilation in litres per minute; vital capacity; complementary air; supplemental air; and maximal breathing capacity. Deductions may also be made from the shape of the curve (Cournand, Richards & Darling, 1939).

The patient is then graded for exercises and joins an appropriate class. Improvement is checked by re-examination, and he progresses to higher grades. Fluoroscopy is of great importance in assessing defects, and areas of deficient ventilation are demonstrated to physiotherapists for special attention. This visual demonstration is of particular value to the rehabilitation staff. Progress is also checked by radiography, physical measurements, and spirographic tracings (the use and analysis of these will be the subject of a later communication by the author). A standard exercise test is also described.

As regards exercises, the first essential is the teaching of correct breathing, and this is started as soon as the patient's physical condition permits. Shoulder and scapula movements, with side-bending and rotating of the chest, develop the accessory muscles and resolve intermuscular and periarthral adhesions.

General exercises and games follow the usual lines, and instructors are trained to notice early signs of distress. In the different classes a competitive spirit is encouraged. To avoid fatigue, afternoons are free for recreation, entertainments and country walks. The author stresses the importance of early rehabilitation.

From a considerable experience, the author believes that a chest rehabilitation centre can restore the majority of patients to a high level of performance in a remarkably short time. Patients should be allowed to go home occasionally during their period at the centre.

REFERENCE

- Cournand, A., Richards, D. W. J. & Darling, R. C. (1939) *Amer. Rev. Tuberc.* 11, 5

277

PULMONARY COMPLICATIONS OF THE COMMON COLD AND SINUSITIS: Findings in Mass Radiography by J. A. Kennedy, *Lancet*, 1, 769-771, 19/6/43

The author reviews 100 examples of transient radiological opacities in patients with the symptoms of a common cold. These shadows were noticed during the routine mass miniature radiographic examination of *Royal Air Force* personnel. The pulmonary shadows were commonly small, and almost always situated in the lower zones of the lungs. They were rarely accompanied by constitutional disturbance and the majority resolved spontaneously within two weeks. Coryza and a slight productive cough were the common symptoms, but 9 of the 100 patients were symptomless. The condition was most common in the winter months from December to May; most patients commenced to have symptoms 7-14 days before the radiographic examination, and only 11 were pyrexial when examined.

The right lung was affected in 49 patients, the left lung in 30, and 21 had bilateral lesions. Only 2 patients had lesions in the upper lobes, the majority being situated in the posterior

part of the lower lobe. Radiographically the lesions were of 3 types, (i) patchy bronchopneumonic shadows, (ii) circumscribed homogeneous opacities, and (iii) increased basal striations. The author suggests that these lesions were due to the inhalation of infected material of low virulence from the upper respiratory tract.

[This condition differs clinically and to some extent radiologically from the primary atypical pneumonia described by Drew, Samuel & Ball (1943). It is probably identical with a condition reported by Ramsay & Scadding (1939) which they called "benign circumscribed pneumonia."]

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- ¹ Drew, W. R. M., Samuel, E. & Ball, M. (1943) *Lancet*, 1, 761
Ramsay, H. & Scadding, J. G. (1939) *Quart. J. Med.* 32, 79
¹ [see *BMB* 281]

278

RADIOLOGY IN POST-OPERATIVE CHEST SURGERY by W. P. Cleland & A. M. Rackow, *British Journal of Tuberculosis*, 37, 55-63, April 1943

The complications which follow operations on the chest are numerous and often require urgent treatment. Diagnosis is made difficult by the fact that the patient is so ill that easy physical examination is often impossible and radiological examination thus becomes of paramount importance. Radiographs of such patients present special problems and these are discussed by the authors. They stress the necessity for taking both true postero-anterior and true lateral views in order to obtain a complete picture of the thoracic contents. Considerable penetration is often necessary, usually 75 to 85 kilovolts, and in many cases where lesions are obscured by fluid or by the heart shadow, a Bucky or stationary grid is an advantage, although this cannot be used if the patient has to be x-rayed in his bed with a mobile unit. The standard teleradiographic distance of 5 feet [about 1.5 m.] should be used whenever possible, and the central ray from the tube should always be horizontal so that fluid levels will be clearly shown.

Operations for the removal of tumours of the chest wall often penetrate the pleura, and there may be a post-operative hemothorax. Tangential radiographs will distinguish between this and a hematoma of the chest wall.

After extra-pleural pneumonolysis, blood and serum may collect and clot in the extra-pleural space. This clot may be mistaken for a collection of fluid but its upper level will not change in position when the patient's posture is altered.

After an upper thoracoplasty combined with an extra-fascial apicolysis, a fluid level will be seen in the space originally occupied by the apex of the lung. Effusion or hemorrhage into this extra-fascial space, with or without infection, produces an opacity in this area, the fluid level is no longer seen, and air is often driven up into the tissue planes of the neck.

The management of collections of pus or fluid in the pleural cavity is one of the most frequent tasks of the thoracic surgeon. In determining the site for aspiration, the postero-anterior film will show the relation of the effusion to the anterior and posterior ends of the ribs, and the lateral film will show its situation in the sagittal plane. From these two views the surface markings of the effusion can be outlined. 15 or 20 cm.³ of iodised oil, introduced through the aspirating needle when an empyema is found, will sink to the bottom and outline the lower limit of the cavity when the patient is in the erect position. This is a useful guide for subsequent drainage. Opaque media such as iodised oil are also of great value in delineating pleural and pulmonary cavities radiographically after surgical drainage has been performed. When the opaque medium has been injected a postero-anterior film is taken in the prone or supine position and a lateral film in the erect position. These will show both the upper and lower limits of the cavity.

If iodised oil is not obtainable, a suspension of barium sulphate 50 parts and arachis oil 50 parts is effective. If a bronchial fistula is present, a thicker suspension must be used which will not enter the bronchial tree; barium sulphate 50 parts and 25 parts each of arachis oil and liquid paraffin is a suitable formula. Before the radiographs are taken the

drainage tube should be replaced by a strip of sterilised leaded rubber of the same length; this will show the relationship of the tube to the cavity.

After operations on the lung such as lobectomy and pneumonectomy, there is usually an effusion of blood and exudate which tends to become loculated owing to the formation of fibrous septa. Penetrating films taken in the postero-anterior and lateral positions are of value in localising these pockets before they are aspirated.

279

MASS RADIOGRAPHY IN WOMEN : A Review of 30,000 Examinations

by F. T. Clive, *Tubercle*, 24, 63-67, April 1943

The subjects of this investigation were all recruits for the Women's Auxiliary Air Force who had previously passed a thorough clinical examination, and this may account for the relatively small number of tuberculous cases discovered. 525 (1.75%) of the 30,000 women showed radiographic evidence of pulmonary tuberculosis and 102 of these had active lesions. Comparing the results of this survey with those obtained by Trail (1942) in an examination of men of the Royal Air Force it is suggested that between the ages of 17 and 20 active tuberculosis is twice as common in women as in men. Inactive lesions become more numerous as the age of the subjects advances, showing that the disease must often heal spontaneously. The total incidence of tuberculous lesions in the lungs is one-third higher in women than in men when all age groups are considered. Of the 102 subjects with active tuberculosis, 14 gave a family history of tuberculosis and 29 had symptoms. In as many as 64 cases, no significant history of any kind was obtainable. In 52, the disease was early and small in extent; in 66, abnormal physical signs were detected and in 18 the sputum contained tubercle bacilli.

The most common non-tuberculous lesions were pneumonia and shadows due to catarrhal infections (13 cases). Various congenital abnormalities were discovered; 32 (0.11%) subjects had a lobe of the azygos vein and no less than 147 (0.49%) had a cervical rib.

The author concludes that, in any mass radiological survey of women, about 3% of the subjects will require further examination with a full size x-ray film, and 4 women out of every 1,000 will require immediate hospital treatment. As an indication of the effect of preliminary selection by a strict physical examination the incidence of active tuberculosis in this series, 0.3%, may be compared with the incidence of 0.63% reported by Banzsky (1942) in a survey of unselected factory workers.

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1 [see *BMB* 43]

280

TUBERCULOSIS SURVEY AT A MENTAL HOSPITAL BY MINIATURE RADIOGRAPHY

by W. E. Snell, J. F. MacMahon & F. R. G. Heaf, *Lancet*, 2, 636-638, 20/11/43

These writers examined 2,035 patients and 224 staff at *Leavesden* Mental Hospital by miniature radiography. Exhaustive clinical and pathological examination of suspects was undertaken. Thirty-six apparently new cases of pulmonary tuberculosis were detected. In addition 87 cases, including 37 with widespread calcification, seemed to have inactive lesions. The total incidence of tuberculosis was estimated at 6%, of which 2% were active. The type of pulmonary tuberculosis demonstrated was of interest. Most of the patients were suffering from congenital mental defects, and were leading an inert, vegetative existence, with depression of motor activity, including respiratory movements and the cough reflex. In many, the disease process seemed to follow a subclinical and comparatively benign course, with spontaneous cure. The lack of symptoms, rareness of cavitation and frank hæmoptysis, the negative bacteriology and the incidence of widespread calcification support this view. From their findings, the writers demonstrate that asymptomatic

cases of pulmonary tuberculosis can be detected by chest x-ray examination. Although the miniature x-ray film proved its value, the routine use of 15 × 12 inch [about 38 × 30 cm.] films would normally seem to be preferable in the case of difficult groups of patients such as those described above; a possible alternative is the 5 × 4 inch [about 13 × 10 cm.] mass-radiography unit for large-scale surveys of mental patients.

281

PRIMARY ATYPICAL PNEUMONIA

by W. R. M. Drew, E. Samuel & M. Ball, *Lancet*, 1, 761-765, 19/6/43

The term "atypical pneumonia" is used to denote pneumonic consolidations other than those caused by any known virus, rickettsia, bacterium or chemical agent. The disease is not new, but the widespread use of radiography, for example in the Armed Forces, especially in influenza-like conditions, is leading to its more frequent recognition. The seasonal incidence of atypical pneumonia differs from that of pneumococcal pneumonia. November, February and March have been noted as the peak months, and its incidence corresponds with that of infections of the upper respiratory tract and the bacterial pneumonias. Young persons are particularly susceptible and the disease spreads by droplet infection. Fatal cases are rare and the pathology has not been studied extensively.

The lesions seem to consist of an interstitial pneumonia and bronchitis with adjoining areas of collapse, consolidation, and emphysema with muco-purulent exudate in the bronchi. Interstitial infiltration with mononuclear cells is a constant finding. The leucocyte count is normal or slightly raised with a relative increase in the mononuclear cells. The erythrocyte sedimentation rate is raised and the sputum contains mononuclear cells in addition to the normal bacterial flora.

The ætiology of atypical pneumonia is unknown but similar pulmonary lesions can be produced in animals by many viruses. In particular the physical, radiological, and pathological findings in pulmonary psittacosis are identical with those of atypical pneumonia and patients with the latter have shown blood antibody responses similar to those found in psittacosis. Andrewes & Mills (1943) have shown that psittacosis is commonly found in pigeons in Britain, and the fact that atypical pneumonia usually affects young people may account for its severity being less than that of psittacosis in older subjects. Attempts to find a relationship between the influenza virus and atypical pneumonia have failed, but similar pulmonary lesions are found in some rickettsial diseases.

The authors describe 50 cases of atypical pneumonia occurring in Service personnel. The onset was usually gradual and was marked either by headache, malaise and aching limbs or by coryza, a painful throat, and retro-sternal soreness. Cough usually developed in from 2 to 5 days. The headache was sometimes so severe that it resembled meningitis. The sputum was muco-purulent and not blood-stained, although small frank hæmoptyses occurred in 3 cases. Pain in the chest on the side of the lesion was fairly common; it was usually continuous and not pleuritic. Dyspnoea and cyanosis were uncommon; there was often a relative bradycardia. Most patients had a pyrexia of 100° to 102° F. [about 38° to 39° C.] which subsided in 7 to 10 days, but some were afebrile throughout. Pharyngitis was common, but there were often no abnormal physical signs in the chest. The average duration of the disease was 33 days and complications such as encephalitis and otitis media were rare.

No relationship was observed between the severity of the clinical findings and the size of the radiological lesion. The lesions were commonly found in the lower lobes and varied in size, rarely involving a whole lobe. In 6 cases the disease was bilateral. The usual radiological finding was an opacity of variable size and indefinite outline, sometimes having a reticulated appearance; the hilar glands were usually enlarged. The lesions can simulate those of acute tracheo-bronchitis, tuberculosis, abscess or resolving pneumococcal pneumonia, especially after inadequate sulphonamide therapy. A small area of bronchiectasis with surrounding consolidation can give a similar picture. All these conditions must be

considered in the differential diagnosis. There is no specific treatment; the patient should be confined to bed during the acute phase. Drugs of the sulphonamide group have no effect on the course of the disease and should not be used.

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Tuberculosis in Children

282

CHILDHOOD INFECTION AND ITS RELATION TO ADOLESCENT AND ADULT PULMONARY TUBERCULOSIS

by A. M. Macpherson, *British Medical Journal*, 2, 98-101, 24/7/43

This is the eighth of a series of reports published by the Research Department of the *Brompton* Hospital during the past 14 years, and it consists of a summary of the previous reports, together with some conclusions which may be drawn from them. The references to the earlier reports are given at the end of this abstract.

Report I (1930) was based on an analysis of the mortality rates from tuberculosis in children in England and Wales between the years 1898 and 1927. It showed the increasing incidence of young adult tuberculosis, although the general mortality from tuberculosis in childhood was improving. In families attending the *Brompton* Hospital, it was found that there was a definitely increased mortality rate from tuberculosis among children under 5 who were living in contact with relatives with a positive sputum.

Report II (1931). During the years 1930 and 1931, 1,220 children were tuberculin-tested and were divided into two groups, (i) those who were known to have been exposed to tuberculosis and (ii) those with no history of contact. The number of positive reactors was almost twice as great in the contact as in the non-contact group. Under the age of 5 years the difference was even more striking, the number of positive reactors being 5 times greater in the contact than in the non-contact group.

Report III (1932). X-ray examination of the tuberculin-positive reactors showed that tuberculous pulmonary lesions of the adult type were rare in children.

Report IV (1933). Re-investigation of some of these children after 1½ to 2 years showed that, whereas the contact children acquired a high degree of tuberculin sensitivity at an early age, the non-contact children did not reach this degree of allergy during childhood.

This work was continued over a number of years and included serial radiography of the children who showed lesions. Finally it was possible to form a fairly complete picture of primary tuberculosis of the lungs in childhood (*Report VII*, 1939). The condition was usually symptomless and healed spontaneously in most cases. Enlargement of the hilar lymph glands sometimes produced complications such as atelectasis. Tuberculous meningitis occurred in a few cases, and there was a striking relationship between the incidence of childhood tuberculosis and exposure to infection.

The occurrence of primary infections in childhood was considered to be a much less serious matter than the high incidence of tuberculosis in young adults, and a separate investigation of this problem has been in progress since 1936. It was noticed that, as the children grew into adolescence, lesions of the adult type began to appear in the lungs. These lesions were usually small and single, often situated at the apex, and rarely gave rise to any symptoms. They showed a tendency to spread and seldom healed spontaneously if untreated, but it was often 3 to 5 years before the patient developed symptoms, and by that time a cavity was usually present. An analysis of 1,000 patients at *Brompton* Hospital who developed pulmonary tuberculosis between the ages of 15 and 25 showed a history of contact infection in 40% (*Report VI*, 1936).

In the majority of instances the disease was far advanced

before the patient sought treatment. It therefore seemed probable that these lesions started as the small, symptomless foci already observed in adolescents, and this view was confirmed by a radiological survey of 2,381 young people between 14 and 21 years old (*Report V*, 1936). This was the first mass radiographic survey to be carried out in Great Britain, and it showed an incidence of pulmonary tuberculosis of 0.65%. Comparison of this figure with the official figures for the incidence of tuberculosis in the general population (0.4% to 0.75%) suggested that the majority of these symptomless infected adolescents must eventually break down and develop extensive disease.

The treatment of a minimal lesion discovered by x-ray examination in the lung of an apparently healthy young person presents a difficult problem. This type of patient does not respond readily to rest and sanatorium treatment, as he is active and feels well, despite the fact that the lesion is slowly spreading. If he is allowed to lead a normal life, it is probable that the diseased area will become adherent and that cavitation will occur, thus reducing the chances of successful treatment.

It is suggested, therefore, that a shallow artificial pneumothorax should be tried as the treatment of choice for controlling a symptomless but progressive tuberculous lesion in the lung of an adolescent. This provides rest for the affected lung and also ensures that the patient is kept under regular observation.

Many such patients have returned to their school or work within a few days of the induction of the pneumothorax and have remained well. It should not be necessary to maintain the collapse for more than 2 or 3 years. The results of this treatment have yet to be seen, but it is advanced as an alternative to other methods such as prolonged rest and sanatorium routine which have proved unsatisfactory and impracticable in cases of this type.

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283

TUBERCULOSIS IN CHILDREN

by J. C. Roberts, *Lancet*, 2, 2-4, 3/7/43

This analysis of 100 consecutive cases at the *Middlesex County* Sanatorium, Harefield, illustrates some of the clinical features and sequelæ of tuberculosis in infants and children. Fifty were found to have a primary complex in the lung, more commonly on the right side. Thirty-five of these had symptoms, the commonest being cough, fever, malaise, lassitude, loss of weight and gastro-intestinal upsets. Erythema nodosum was noted in 5 cases. Perifocal infiltration of the lung around the primary lesion was often well marked, and in other cases there was pulmonary collapse due to bronchial obstruction by the enlarged glands (epituberculosis). In some cases the parenchymal infiltration in the lung had spread and there was cavity formation.

Of the patients who did not have radiological evidence of a primary complex in the lung, 14 had pleural effusions, 8 had pulmonary tuberculosis of the adult type, 7 had cervical adenitis, and 3 showed signs of tuberculous peritonitis. The lesions of the adult type responded well to collapse therapy.

The author emphasises that the occurrence of a primary complex in a child usually causes symptoms; it should be recognised and treated carefully in an institution. The importance of careful and repeated examination of children who are known to have had contact with an infected adult is also stressed. There was a history of such contact in 60% of this group of tuberculous children.

INCIDENCE AND TREATMENT OF TUBERCULOSIS IN CHILDREN

by G. B. Fleming, *Lancet*, 2, 580-581, 6/11/43

It is not generally recognized that, in children dying of tuberculosis, by far the most usual route of infection is through the respiratory tract. The majority of children become infected with tuberculosis, but only a small proportion of these under one year old give a positive Mantoux reaction; as age increases, however, positive skin reactions become more and more frequent, so that at the age of twelve 50%, and at twenty 70% are positive. The incidence of tuberculous meningitis, the usual cause of death in such cases, falls with increasing age. The present paper, from the Department of Pædiatrics, University of Glasgow, and the Royal Hospital for Sick Children, Glasgow, reports that of 326 children dying of tuberculous meningitis, 70% were under four years old, while of 322 over seven years of age only 5% died. The writer makes the important points that (a) the majority of children are infected from a human source, and (b) the younger the age at which infection takes place, the greater the risk. Young children should be protected from infection. Those giving a positive tuberculin skin reaction should be removed to suitable surroundings and kept under observation for six months.

Social and Statistical Aspects of Tuberculosis

285

TUBERCULOSIS IN PEACE AND WAR

by A. S. MacNalty, *Tubercle*, 23, 263, December 1942

This paper, the author of which was until recently Chief Medical Officer to the Ministry of Health, contains a survey of the development and present position of tuberculosis services in Britain. In 1841 the *Brompton* Hospital was founded, in London, for the treatment of the tuberculous. In 1887 Sir Robert Philip started at Edinburgh the first Tuberculosis Dispensary or clinic for tuberculous patients who were not confined to bed. In 1912 the National Tuberculosis Service was established. Under this scheme each County Council, or County Borough Council, undertook to provide treatment for all forms of tuberculosis in its area, and dispensaries, sanatoria and hospitals were set up for this purpose. The scheme had only just started when, in 1914, war was declared.

The British Isles suffered less from direct enemy action than in the present war, but, even so, the tuberculosis death rate rose from 988 per million in 1914 to 1,498 per million in 1918. This was largely due to overcrowding and lowering of resistance through physical and mental strain; long hours of work in munition factories and a lowered standard of nutrition also contributed. In addition, the Tuberculosis Service was restricted owing to shortage of medical staff and restrictions on the building of sanatoria.

The years of peace following 1918 were remarkable for many advances in the treatment of tuberculosis in Britain. These included the rise of thoracic surgery, improved radiological technique, and the foundation of Village Settlements. At the outbreak of the present war the mortality from all forms of tuberculosis in Britain was declining, and this improvement was steadily maintained year by year and was especially marked among the young adult population.

Since 1939 the expected war-time increase in tuberculosis has taken place; the mortality rate rose from 26,250 in 1939 to 28,619 in 1941. It has been calculated that the increase amounted to 6% in the first year and 10% in the second year of the war, and there has been a serious rise in the mortality from tuberculous meningitis.

There are many factors to account for these figures. Mass radiographic surveys in the Fighting Services¹ have shown that 1.3% of Naval personnel and 1.74% of Army personnel have radiological evidence of pulmonary tuberculosis, while about 0.3% have active disease. At the outbreak of war, evacuation from the cities tended to spread the tuberculous population into other areas where there were not adequate

means for treating them. Many hospitals have been bombed. An acute shortage of nurses has developed owing to the great demands of the Services and of industry, and this has caused a reduction in the beds available for the treatment of tuberculosis. Overcrowding has occurred both in air raid shelters and in homes owing to black-out conditions; this probably also accounts for the increase of tuberculosis in mental hospitals. These are the chief reasons for the spread of tuberculosis during the present war.

Great efforts are being made to check this process. Lack of protective foods, fruits, vegetables, cheese, eggs and milk, may lower the general resistance in war time, and the diet is therefore being carefully planned. Milk supplies are being watched, particularly with regard to the control of infected cattle and pasteurisation of milk. Attempts are being made in factories to control the factors which lead to an increase in tuberculosis: these are overcrowding, employment of the unfit, employment of those unused to manual work, fatigue and deficient ventilation.

The author advocates the adoption of the following immediate measures for the prevention and treatment of tuberculosis:

i. The widespread use of mass radiography, particularly in industry, in order to facilitate early diagnosis. This is already being undertaken by the Ministry of Health.

ii. The provision of more hospital and sanatorium beds for the treatment of patients diagnosed by mass radiography.

iii. The development of Village Settlements. Such Settlements provide expert treatment for all forms of tuberculosis and work for those patients who are capable of it. They also provide the patient with a normal community life while segregating him from the general population. During the 25 years since the founding of the first Settlement by the late Sir Pendrill Varrier-Jones at Papworth, *no child born at the Settlement has contracted tuberculosis while living there*. This proves conclusively that spread of the disease can be prevented under the conditions which prevail in a Settlement. These include proper hygienic precautions, adequate food, good housing, absence of anxiety, freedom from strain and the risk of unemployment, prompt treatment of relapses, and continuous medical supervision. Four Settlements of this type are already in existence, more are needed, and this kind of rehabilitation for the tuberculous should also be extended by the provision of special workshops where workers can be kept under medical control.

286

THE COMPREHENSIVE ATTACK ON PULMONARY TUBERCULOSIS

by A. S. MacNalty, *British Medical Journal*, 2, 599-601, 13/11/43

This is the second Memorial Lecture to Sir Pendrill Varrier-Jones, founder of the Papworth Village Settlement for the tuberculous. The author enunciates certain principles for the guidance of the physician in the appropriate use of hospitals and sanatoria, and in the selection of tuberculous patients for different forms of treatment. At Papworth the tuberculous subject remains under constant medical, psychological and social supervision.

A greater incidence of pulmonary tuberculosis is to be expected at the end of the present war, and the Ministry of Labour has inaugurated a Scheme for Training and Re-settlement of Disabled Persons, in which certain types of tuberculous subjects are included. In outlining the pioneer work of Varrier-Jones, MacNalty records what is being done by the Government towards the rehabilitation of the tuberculous after the war and indicates the lines upon which further development is an urgent necessity.

287

RESPIRATORY TUBERCULOSIS: Effect of the War on the Length of the Interval between Notification and Death

by E. Lewis-Fanning, *British Medical Journal*, 2, 684-685, 27/11/43

In areas of England and Wales generally, the level of mortality from pulmonary tuberculosis in 1940-1941 was higher than in the years immediately preceding the war. In this report an attempt is made to measure to what extent the excess—at least in the administrative county of Middlesex—was due

¹ [For the results of such a survey in the Royal Air Force, see *BMB* 43.]

to a shortening of the duration of the disease brought about by lowered resistance in those already infected.

At all ages combined it was found that deaths occurring from pulmonary tuberculosis in the three pre-war years 1937-39 and in the two war years 1940-41 were distributed according to the interval between notification and death in the following proportions:

Interval in years	Males		Females	
	1937-39	1940-41	1937-39	1940-41
	%	%	%	%
Under 1	541 43	398 42	384 41	303 46
1 -	561 44	390 41	426 46	275 41
5 +	169 13	156 17	120 13	88 13
All durations	1271	944	930	666

No statistically significant change in the percentage dying in the duration-groups in the two periods can be demonstrated for either sex. It is argued that if lowered resistance due to the war had brought about some increase in mortality in 1940-41 from the death in those years of patients who otherwise might have lived to 1942 or later, some disturbance in the percentages would have appeared. (No change would occur had such an increase been equally effective at each duration-group, but this is a highly improbable supposition.)

The analysis was applied not only to deaths at all ages combined, but to the deaths in age-groups. The results when tested statistically were inconclusive, but suggested a small increase in the proportion of patients dying with durations of the disease of five years and over, accompanied by a decrease in the proportion with durations of one to five years.

The author makes a comparison between the pre-war and war years as regards the average length of duration in age-groups. No differences greater than might be expected from the play of chance were found and he concludes that "the analysis produced no conclusive evidence of any appreciable decrease in the average length of time between notification and death in the two years following the outbreak of war."

A word of caution should perhaps be given against accepting this result for Middlesex as generally applicable to other areas of England and Wales. The number of deaths per annum studied is relatively small and for larger areas, aggregates of areas, or industrial areas, significant differences might appear which would warrant contrary conclusions. However that may be, the work is valuable if only that it satisfies a long-felt need by supplying some indication of the pre-war distribution of deaths from pulmonary tuberculosis according to duration of disease.

288

SURVIVAL RATES IN PULMONARY TUBERCULOSIS
by B. C. Thompson, *British Medical Journal*, 2, 721, 4/12/43

This paper is a continuation of earlier work (Thompson, 1942) on survival rates of tuberculous patients with positive sputum, in the county of Durham. It might perhaps have been stated that the initial investigation covered a period when housing was being condemned and replaced under Slum Clearance Orders, when chronic unemployment prevailed and mines were completely closed down, so that economic depression was general and family incomes were low.

The original material consisted of 406 patients, all over 10 years of age, with pulmonary tuberculosis with positive sputum notified in the Chester-le-Street tuberculosis dispensary area of the county of Durham, during the years

1928-1938 inclusive. The histories of these patients were traced from the date of diagnosis at the dispensary until either the anniversary of that date in 1941, or until the death of or loss of contact with the patient, whichever occurred first.

In this later article the same 406 patients have been traced wherever possible to the anniversary of diagnosis in 1943, an additional two years. Clearly, those entering the experience in 1938 can now have been followed up for five years, originally for only 3.

By utilising the life-table method the probabilities (i) of dying each year after diagnosis, (ii) that having survived a given number of years the patient would survive a further five years, were calculated. The results of the extended analysis confirm and amplify the original.

Of 100 sputum-positive patients, 40 die within a year of diagnosis. Little more than a quarter remain alive at the end of five years and about an eighth at the end of ten years. There is an even chance that patients who survive the first five years will not live another five years, but it may be safely considered that those who do have made a sure recovery. Those within age-group 30-39 have the most favourable chance.

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289

TUBERCULOSIS IN LONDON

by W. A. Daley & B. Benjamin, *British Medical Journal*, 2, 712-713, 4/12/43

During the period between the two world wars, both the incidence and mortality from pulmonary and non-pulmonary tuberculosis in the administrative county of London steadily declined, as judged by the trend of notification and death rates. Following the outbreak of war in 1939 the decline gave place to an increase. In this paper the authors have extended their previous study (Daley & Benjamin, 1942) of that change by the addition of figures for 1942. The results show a definite contrast between children and adults.

At ages under 15 the notification rate, which in 1941 was about three times the 1938 level, fell to approximately only twice that figure. The death rate, which in 1941 was about 400 % higher than 1938, fell in 1942 to nearly the pre-war level. The numbers involved at these ages are small, and too much significance should not be attached to the results. A similar picture is presented as regards non-pulmonary tuberculosis.

Amongst adults, on the other hand, the incidence continued to increase in 1942. Mortality declined slightly for the pulmonary, but increased for the non-pulmonary type. The notification rate in 1941 for pulmonary tuberculosis was 124 % of the 1938 figure; in 1942, 130 %. Death rates fell from 151 to 136 % for pulmonary, but increased from 150 to 167 % for non-pulmonary cases. It is considered possible, as pointed out by Stocks (1942), that any decline in mortality found in 1942 may be only temporary.

Discussing the contrasts shown between children and adults, the authors suggest two reasons for the lower incidence found in 1942 amongst children. First, that the return from evacuation areas of healthy children reduced the proportion of tuberculous to the total number of children in the County of London, and secondly that the substantial reduction of living in air-raid shelters had a beneficial influence. The continued increase in incidence amongst adults, it is suggested, is associated with the undiminished pressure of war production, the effects of black-out on ventilation, and the shortness or lack of holidays.

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Stocks, P. (1942) *Brit. med. J.* 2, 750

BOOKS, MEMORANDA, REPORTS

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290/1

MASS MINIATURE RADIOGRAPHY

by R. R. Trail, H. G. Trenchard & J. A. Kennedy. London, J. & A. Churchill, 1943. 96 pages ; 24 illustrations. 8s. 6d. [£0.425]

The authors of this little book write from a large practical experience of mass examination of the chests of Royal Air Force personnel. The setting up and administration of a mass miniature radiography department are discussed and the necessity for the high technical quality of the miniature radiograph is emphasized. Accommodation, apparatus, lay-out and staff, records and the disposal of suspects are other matters carefully dealt with, and there are sections devoted to the interpretation of films, classification, record cards and accessory equipment. The book appears at a time when mass radiography centres are being organized throughout Britain. It should be of value in the organization and running of such centres.

290/2

CHEST EXAMINATION : The Correlation of Physical and X-ray Findings in Disease of the Lungs

by R. R. Trail. London, J. & A. Churchill, 1943. 107 pages ; illustrated. 10s. 6d. [£0.525]

The main purpose of this book is to correlate the anatomy and pathology of the lungs with the physical findings—clinical and radiological. There is a summary of the anatomy and normal radiological appearance of the lung, a section correlating the abnormal physical and radiological findings in common chest diseases with the pathology, and some notes on physical signs and on reading films of abnormal chest conditions.

290/3

THE RADIOLOGICAL APPEARANCES OF EARLY PULMONARY TUBERCULOSIS. Ministry of Health Memorandum No. 268

by R. R. Trail & P. Kerley. London, H.M.S.O., 1943. 8 pages. 2d. [£0.008]

The memorandum has been written jointly by a chest physician and a radiologist. In a short introductory note, Sir W. Wilson Jameson, Chief Medical Officer to the British Ministry of Health, refers to the need created by the development of mass radiography for a standard technique and the systematic study of abnormal radiographical appearances. In the first two pages, the essentials of a good postero-anterior radiogram of the chest are defined and the necessary equipment and technique are discussed. The remainder of the memorandum is devoted to a description of the varying radiological appearances in early pulmonary diagnosis. This section is illustrated by 21 small diagrams.

290/4

CARE OF TUBERCULOSIS IN THE HOME

by J. Maxwell. London, Hodder & Stoughton, 1943. 105 pages. 7s. 6d. [£0.375]

This is a résumé of the essential points about tuberculosis and its effect on the social life of the patient, for whom it is written. The writer recommends that each step in treatment be explained to the patient, who should learn to control his own life and retain a healthy attitude towards his disease. There are chapters on the nature, symptoms and treatment of tuberculosis, on hygiene and prevention, and advice on occupation, marriage and diet. This book should prove a helpful guide to the tuberculous patient, both during his illness and on his return to working life, and also to the general practitioner who shares responsibility for his care.

290/5

MEDICINE IN BRITAIN

by H. Clegg. London. Published for the British Council by Longmans, Green & Co., 1943. 46 pages ; 7 illustrations. 1s. [£0.05]

If even the informed foreign observer is often unable to discern a coherent pattern in the multiform edifice of British Medicine, it must be conceded that there is good reason for his difficulty. The

multiplicity of medical degrees and diplomas, and of agencies concerned directly or indirectly with medical education and with the promotion of health in the school, in the home and in the factory, may sometimes seem to defy rational interpretation. In this book, British Medicine is compared to a network of English country roads. It might as aptly be compared to a large old house, to which, in response to the changing needs of successive generations, have been added bathrooms, electric light, central heating and, at different periods, modern structural extensions.

Dr. Clegg has succeeded brilliantly in his difficult task of surveying British Medicine and explaining the evolution and purpose of its parts. His small book contains a wealth of authoritative information which is presented in the easily readable style of a natural writer. The function and character of the General Medical Council, the Medical Corporations (of which the Royal Colleges of Physicians and of Surgeons are examples), the Medical Research Council, the Ministry of Health, the British Medical Association, the "Voluntary" Hospitals, and other important institutions are clearly explained in the light of their historical development. The essential facts about National Health Insurance, industrial medicine, the tuberculosis services, the Indian and Colonial Medical Services, and such wartime developments as the Emergency Medical Services and the Emergency Public Health Laboratory Service are included.

Although the final impression on the reader is one of cumulative progress, there is now in Britain an almost unanimous recognition of the need for substantial changes in the organisation of the medical services. Dr. Clegg's last chapter is a useful short statement of the differing views of the profession on this important question.

A "white paper" containing the proposals of the Ministry of Health for the future of British Medical Services has just been published by the British Government. These proposals will be freely discussed, and the medical profession will expect and has been promised ample opportunity for their consideration and criticism. As an aid to the understanding of the coming discussions of British medical services, "Medicine in Britain" should be invaluable. It should also be an indispensable handbook to the overseas medical visitor to Britain, or to medical men in other countries who wish to acquire without undue effort an integrated conception of British Medicine at a moment when it is at the threshold of great changes.

290/6

RECENT ADVANCES IN MEDICINE

by G. E. Beaumont & E. C. Dodds. 11th edition. London, J. & A. Churchill, 1943. 18s. [£0.9]

This well-written survey of recent medical progress, the pioneer of the "Recent Advances" series, has attained its eleventh edition in nineteen years. The new edition has been enriched by the addition of new material on penicillin, the sulphonamides and vitamins, blast injuries of the lungs, "acid" phosphatase, plasma protein regeneration and amino-acid therapy, the blood groups, the Rh factor, the dangers of blood transfusion, and thymectomy in myasthenia gravis. Methods for sulphonamide estimation in blood and urine are given, and additional notes are made on the treatment of hæmatemesis and on the use of the continuous intragastric drip for certain types of peptic ulcer. The sex-hormone chapter has been revised, and additions to the kidney chapter include descriptions of the specific gravity and inulin clearance tests, the compression syndrome, and the dangers of mercurial diuretics. As in earlier editions, the book is liberally supplied with references to recent literature, and it will prove especially valuable to the physician who wishes to keep abreast of the most recent developments of clinical and laboratory medicine.

290/7

FRACTURES AND JOINT INJURIES

by R. Watson-Jones. Third Edition. 2 vols. Edinburgh, E. & S. Livingstone, 1943. 960 pages ; 745 illustrations. £3 15s. [£3.75]

This is one of the most important books on the subject which has appeared in the English language, and it should be of the utmost value, not only to the orthopaedic surgeon, but to the general practitioner who is called upon to treat bone and joint injuries. The book reveals the writer's talent for teaching and for original and stimulating presentation of his matter ; the illustrations are many and are of an extremely high standard, and it is evident that much thought has been devoted to their selection. This comprehensive work includes sections on open and infected fractures and war wounds, chemotherapy and the closed plaster technique. The subject of rehabilitation, of which the author has been a pioneer, is also fully covered. Amputations and their indications are carefully dealt with. The writer, who is Consultant in Orthopaedic

Surgery to the Royal Air Force and a member of the War Wounds Committee of the Medical Research Council, has been intimately concerned with developments in his subject during the present war.

290/5

THE SURGERY OF REPAIR : INJURIES AND BURNS

by D. N. Matthews. Oxford, Blackwell Scientific Publications, 1943. 386 pages ; 198 illustrations. £2 5s. [£2.25]

This book deals with the treatment of the common war injuries which come within the province of the plastic and maxillo-facial

surgeon. Orthopædic surgery is not considered, but the routine immediate treatment of thoracic and abdominal perforating wounds is included because these injuries frequently complicate plastic and maxillo-facial cases in wartime. The methods and treatment described are those used by the author, who has had considerable experience of the subject as Surgical Specialist to the Royal Air Force Voluntary Reserve and Surgical Officer in Charge, Royal Air Force Plastic Unit. Part I of the book deals with shock, crush injury, chemotherapy, anaesthesia, the surgery of wounds, nerve and tendon suture, abdominal and thoracic injuries ; part II describes late repair, including scar excision and skin transplants, and nerve and tendon injuries ; part III discusses the repair of facial injuries, and includes descriptions of operations for dealing with the nose, lips, eye, cheek, etc. ; and part IV is an adequate summary of the treatment of burns.

291

GUIDE TO THE JOURNALS

British Journal of Industrial Medicine

1 : January 1944

- The evolution of an industrial society. (M. Greenwood) 2-6
Some aspects of sick absence in industry. (H. H. Bashford) 7-10
Chronic carbon tetrachloride intoxication. (A. Stewart & L. J. Witts) 11-19
The investigation of toxic hazards. (M. W. Goldblatt) 20-30
Heating and ventilation : requirements and methods. (T. Bedford) 31-47
Nutrition and the industrial worker. (E. H. Capel) 48-53
Some foot faults related to form and function. (W. S. Creer) 54-61

British Journal of Radiology

17 : January 1944

- The diagnosis, classification and treatment of tumours of the salivary glands. Symposium (R. T. Payne, C. G. Binnie, J. Munk, F. Roberts, G. T. Calhoun) 13-17
Venous intravasation during 18-24
Malignant tumours of the upper 18-24
The time intensity factor in X-ray irradiation. (E. Paterson) 26-30
Salivary calculus or tartar. (A. S. Johnstone) 31-32

17 : February 1944

- An enquiry into the causation and characteristics of cephalæmatomata. (J. B. Hartley & C. W. F. Burnett) 33-41
Regression of tumours following treatment by stilbæstrol and X-ray therapy, with notes on a case of breast tumour which regressed with stilbæstrol alone. (G. C. Binnie) 42-45
A dosage system for linear gamma-ray sources. (D. E. A. Jones) 46-47
X-ray appearances in anæmic hepatitis. (J. Munk) 48-53
The nature and functions of the intervertebral discs. (F. Roberts) 54-59
Cholecystography : pheniodol as a medium for the Graham-Cole test. (G. T. Calhoun) 60-61

British Journal of Surgery

31 : January 1944

- The Anglo-American Canadian surgical mission to Russia, July, 1943. (G. Gordon-Taylor) 205-207
Military surgery in the "Middle East." (A. E. Porritt) 208-221
Compound fronto-orbital fractures : eight cases. (J. Schorstein) 221-230
Recurrent hernia : an investigation of the causes of recurrence and the application of the principles of treatment of the primary lesion. (W. Patrick) 231-239
A case of cerebrospinal fever with thrombosis of the right axillary artery, followed by gangrene of the right arm, necessitating amputation. (A. Levin & D. M. McElroy) 240-242
Humero-radial synostosis. (E. Frankel) 242-245
Spinal anaesthesia in the treatment of Hirschsprung's disease : with reports of twelve cases. (M. Hawksley) 245-252
Fractures and dislocations of the cervical spine. (F. Crooks & A. N. Birkett) 252-265
On severe intestinal hæmorrhage due to myomatous tumour of the jejunum : with a note on bleeding myomata of the small intestine. (G. Gordon-Taylor) 266-269
Multiple cavernous hæmangiomas of the lungs successfully treated by local resection of the tumours. (R. M. James) 270-272
Congenital dislocation of the shoulder. (G. Flavell) 272-275
Mesenteric defects. (E. G. Dolton) 275-277
Fractures of the triquetrum. (J. G. Bonnin & W. P. Greening) 278-283
Ureteral stricture with perinephric urinary extravasation, caused by metastases from a silent carcinoma of the stomach. (J. D. Fergusson) 283-286
The surgical aspects of sulphapyridine anuria. (J. M. Campbell) 286-288
Post-operative respiratory complications following unilateral inguinal herniorrhaphy in war time : a study of 438 service cases. (B. G. B. Lucas) 288-291
Healing of experimental wounds of lung. (G. L. Montgomery) 292-299

British Medical Journal

1 : 1/1/44

- The nature of concussion. (G. Jefferson) 1-5
Nutritional deficiency in the pathogenesis of disease. (J. Yudkin) 5-7
The prisoner-of-war mentality : its effect after repatriation. (P. H. Newman) 8-10
A case of aspirin poisoning. (A. D. Charters) 10-11
Prostigmin in the treatment of delayed period. (E. Friedmann) 11-12
The chronic medical case in the army. (J. W. Todd) 19-20

1 : 8/1/44

- Gunshot wounds of the head in the acute stage. (H. Cairns) 33-37
Burns and scalds in children : an investigation of their cause and first-aid treatment. (A. W. Wilkinson) 37-40
Heat in the treatment of shock. (A. W. Kay) 40-41
Influenza "A" : an account of a minor epidemic. (T. H. Donnelly, H. P. Hughes, D. Robertson & E. Philipp) 42-43
Estimation of hæmoglobin by photo-electric absorptiometers. (J. M. Peterson & D. H. Strangeways) 43-44
The modern treatment of gonorrhœa in the female. (T. E. Osmond) 51-52

1 : 15/1/44

- Clinical features and treatment of malaria in British troops in West Africa. (S. B. Hughes & R. R. Bomford) 69-73
Despeciated bovine serum (D.B.S.) : a substitute for human plasma. (F. R. Edwards) 73-76
Treatment of anaemia in school-children with iron and ascorbic acid. (L. S. P. Davidson & G. M. M. Donaldson) 76-77
The influence of supplements of vitamins A, B₁, B₂, C, and D on growth, health, and physical fitness. (E. R. Bransby, J. W. Hunter, H. E. Magee, E. H. M. Milligan & T. S. Rodgers) 77-78
Umbilical hernia in children : with special reference to injection treatment. (M. J. Bennett-Jones) 78-79

1 : 22/1/44

- Emphysema of the lungs. (R. V. Christie) 105-108
Supervision of pregnant women in factory employment. (J. V. O'Sullivan & L. B. Bourne) 108-110
Five cases of jaundice following transfusion of whole blood or human plasma. (R. E. Steiner) 110-111
Histological effects of mixtures in the rabbit : some experimental observations. J. K. Beck) 112-113
Vaccination against typh 114
Treatment of pediculosis capitis. (E. Blackstock) 114-115

1 : 29/1/44

- Localized subcutaneous edema with weakness of limb muscles : a syndrome due to polyarteritis nodosa. (R. MacKeith) 139-142
Emphysema of the lungs. (R. V. Christie) 143-146
Infant feeding in relation to mortality in the city of Belfast. (J. Deeny & F. T. Murdock) 146-148
An unusual case of cerebral malaria. (C. S. D. Don & P. F. Meyer) 149
Effects on rats of prolonged feeding with the staple African diet. (J. Gillman) 149-150

1 : 5/2/44

- Some principles of reform in medical education. (F. M. R. Walshe) 173-176
Pethidine as an obstetric analgesic : a report on 150 cases. (B. Gallen & F. Prescott) 176-179
Obstetric analgesia with pethidine. (W. Spitzer) 179-181
Bone marrow as a site for the reception of infusions, transfusion, and anæsthetic agents : a review of the present position. (H. Bailey) 181-182
Staphylococcal septicæmia treated with sulphadiazine. (H. B. Norman) 183
Spontaneous rupture of abnormally mobile spleen. (J. Dubash & G. F. Langley) 183-184

1 : 12/2/44

- Studies on hepatic dysfunction. I. Carbon tetrachloride poisoning. (J. Beattie, P. H. Herbert, C. Wechtel & C. W. Steele) 209-211
A clinical evaluation of some tests of liver function. (G. Higgins, J. R. P. O'Brien, A. Stewart & L. J. Witts) 211-215
Some uses for dry cold therapy, and a proposed cooling cabinet. (W. G. Bigelow & E. C. G. Lanyon) 215-217
Ætiology of "immersion foot." (B. W. Goldstone & H. V. Corbett) 218-219
External prophylactic version (M. B. Trubkowitz & B. A. Archangelsky) 220

Edinburgh Medical Journal

51 : January 1944

- Localised arterial thrombosis of indeterminate origin. (J. R. Learmonth, W. Blackwood & R. L. Richards) 1-20
The protective diet. (R. Pybus) 21-38
The uses and abuses of the female sex hormones. (T. N. MacGregor) 39-55

Journal of Hygiene

43 : January 1944

- Observations on an epidemic of paratyphoid fever in Dundee, 1941. (W. A. Davidson & J. Brodie) 219-228
Human pulmonary tuberculosis of bovine origin in Great Britain. (A. S. Griffith & W. T. Munro) 229-249
Diabetes mortality in 1861-1942 and some of the factors affecting it. (P. Stocks) 242-247
Concentration of the carcinogenic material in a Venezuelan spindle cell by simultaneous molecular distillation and chromatographic adsorption. (J. M. Twort & R. Lyth) 248-251
The prophylactic effect of a colloid material on the skins of mice painted with various types of carcinogenic agents. (J. M. Twort & R. Lyth) 252-255
Hæmolytic streptococci in the dust of hospital wards, and their relationship to infection. (D. G. F. Edwards) 256-265
An agglutinin common to certain strains of lactose and non-lactose-fermenting coliform bacilli. (Lord Stump & D. M. Stone) 266-272
Some observations on accidental vaccinations on the hands of workers in a vaccine lymph institute. (E. S. Horgan & M. A. Haseeb) 273-274
Studies in the dynamics of disinfection. I. New data on the reaction between phenol and *Bact. coli* using an improved technique, together with an analysis of the distribution of resistance amongst the cells of the bacterial populations studied. (R. C. Jordan & S. E. Jacobs) 275-289

Lancet

1 : 1/1/44

- Traumatic arterial spasm. (S. M. Cohen) 1-6
 Reactive anxiety and its treatment. (G. Garmany) 7-9
 Controlled external pressure and oedema formation. (R. J. Rossiter & note by R. A. Peters) 9-11
 Late results of perforated peptic ulcer. (C. P. G. Wakeley) 11-12
 Perforation of gastric and duodenal ulcers: a series of 312 cases. (S. C. Raw) 12-14
 Perforated peptic ulcer during the period of heavy air-raids. (C. C. Spicer, D. N. Stewart & D. M. de R. Winser) 14
 Continuous intravenous adrenaline in spinal anaesthesia for the control of blood-pressure. (F. Evans) 15-17
 Unusual case of pellagra. (T. L. C. Henderson) 17
 Kala-azar in an English seaman. (R. B. Thompson) 17-18

1 : 8/1/44

- Sulphonamide dermatitis: sensitisation from local application. (B. C. Tate & I. Klorfain) 39-44
 Gunshot wounds of the fronto-orbital region. (J. Schorstein) 44-47
 Tender muscles in sciatica: electromyographic studies. (F. A. Elliott) 47-49
 Phemeride: a new antiseptic detergent. (C. N. Iland) 49-51
 Deposit in Seitz-filtered serum (G. E. C. Francis, G. A. Harrison & L. E. R. Picken) 51-52
 Convulsions under anaesthesia treated by change of posture. (A. Smith) 52

1 : 15/1/44

- Hand infections treated with penicillin. (M. E. Florey & R. E. O. Williams) 73-81
 Rehabilitation of the chest case. (F. R. Edwards) 81-84
 Some sensory effects of wounds. (H. Burrows) 84-85
 Myelogenous leukaemia complicating pernicious anaemia. (P. B. Woolley) 85-86
 Acute thyrotoxic bulbar palsy. (L. P. E. Laurent) 87-88
 Orthopaedic surgery and the future. (H. Platt) 95-97
 Evolution of an information service: The Bureau of Hygiene & Tropical Diseases. (R. L. Sheppard) 97-98

1 : 22/1/44

- Endemic goitre in England: argument for preventive action. (Memorandum of the Goitre Subcommittee, Medical Research Council) 107-109
 Forward surgery in a battle period. (G. K. Harrison) 109-111
 Intrapelvic rupture of urethra. (B. C. Murless) 111-112
 Identity of patulin and claviformin. (E. Chain, H. W. Florey & M. A. Jennings; with a note on the crystallography by D. Crowfoot & B. Low) 112-114
 Removal of ether vapour during anaesthesia. (H. G. Epstein) 114-116
 Sciatica: a study of 40 cases. (A. D. Le Vay) 116-118

1 : 29/1/44

- Psychosomatic casualties in the Middle East. (A. Torrie) 139-143
 Triffin nail and plate for peritrochanteric fractures. (G. K. McKee) 143-145
 Haemolytic disease in the newborn: the Rh factor. (F. A. Langley & F. Stratton) 145-148
 Diabetogenic action of alloxan. (H. Hughes, L. L. Ware & F. G. Young) 148-150
 Notes on typhus fever in the Middle East. (W. Brockbank & S. R. F. Whittaker) 150-151
 Portal pyaemia with recovery. (N. Alders) 151

1 : 5/2/44

- Erythroblastic anaemia of childhood (Cooley's anaemia) in Cyprus. (A. L. Fawdry) 171-176
 Postnasal swab in diagnosis of pertussis. (R. Cruickshank) 176-177
 Apparatus for administering oxygen. (W. I. Card, W. J. Griffiths & B. A. McSwiney) 177-179
 Thiourea causing granulopenia and thrombopenia. (P. B. Newcomb & E. W. Deane) 179
 Vitamin-C nutrition in a hospital; with observations on a case of scurvy. (F. T. G. Prunty & C. C. N. Vass) 180-182
 Meniscectomy in soldiers; review of cases discharged from an army convalescent depot. (J. J. R. Duthie & J. G. Macleod) 182-183

1 : 12/2/44

- Anaerobic infections in Tripolitania and Tunisia. (D. M. MacLennan) 203-207
 Supplementary feeding in pregnancy. (M. I. Balfour) 208-211
 Adolescent kyphosis. (T. J. B. A. MacGowan) 211-214
 Rhesus antibody in Rh-positive mother causing haemolytic disease of newborn. (A. J. McCall, R. R. Race & G. L. Taylor) 214-215
 Fitting industry to human needs: the contribution of medicine to industrial well-being. (T. A. Lloyd Davies) 223-225

Medical Officer

71 : 8/1/44

- Growth of infants in the first year of life: a comparison between war years as compared with pre-war years in the town of Glossop. (E. Lewis-Faning & E. H. M. Milligan) 13-15

71 : 15/1/44

- Growth of infants in the first year of life: a comparison between war years as compared with pre-war years in the town of Glossop. (E. Lewis-Faning & E. H. M. Milligan) 21-23

71 : 22/1/44

- Growth of infants in the first year of life: a comparison between war years as compared with pre-war years in the town of Glossop. (E. Lewis-Faning & E. H. M. Milligan) 29-31

ERRATUM: VOL. 2, NO. 1

In line 17 of *BMB* 239 the number 26 was accidentally inserted and should be disregarded

British Medical Bulletin is published by the British Council. One volume will appear each year, and each volume will contain a maximum of 12 parts, issued at approximately monthly intervals. The object of the Bulletin is to provide a guide to medical work in Britain. Requests for further information on any of the investigations reported, or for general information, bibliographies, and particulars of medical books and journals published in Britain should be addressed to the British Council, Medical Department, 3 Hanover Street, London, W.1, England

BRITISH MEDICAL BULLETIN

Vol. 2. (1944)

No. 3-4

SPECIAL CONTRIBUTIONS

CLINICAL EVALUATION OF NEW REMEDIES

by Dr. F. H. K. Green 58

AROMATIC DIAMIDINES IN PROTOZOAL INFECTIONS

by Professor Warrington Yorke 60

RECENT WORK ON THE PHARMACOLOGY OF SULPHONAMIDES

by Dr. F. Hawking 64

BIOLOGICAL STANDARDISATION OF NEOARSPHENAMINE

by Dr. F. Hawking 70

REVIEW OF SELECTED PAPERS

Modes of Drug Action

Biological Aspects : Antagonism of Drugs 71

Antimalarials : Cell Metabolism 72

Blood-Brain Barrier : Drugs used in Sleeping Sickness 72

Narcotics and Amphetamine : Central Nervous System Metabolism 73

Chemotherapy : Relations between *In vivo* and *In vitro* Actions 74

Physico-Chemical Aspects 74

Chemical Constitution and Pharmacological Action 75

Chemical Structure of Arsenicals : Drug Resistance of Trypanosomes 75

Insecticidal Action : Drug Reactivity—Phase Distribution Relationships 75

Physical-Chemical Properties of Biologically Active Molecules 75

Benzpyrene : Possible Mode of Action as a Carcinogen 76

Variations in *Bact. Lactis Aerogenes* and Change of Medium 76

Resorcinol and *m*-Cresol : Growth of *Bact. Lactis Aerogenes* 76

Adaptation of *Bact. Lactis Aerogenes* to Sulphonamides 76

Antimalarials

Drug Control of Malaria 76

Effects on Electrocardiograms 77

Activity in Man, Monkey and Bird 77

African Cinchonas : Avian Malaria 77

Mepacrine and Arsenic-Resistance of Trypanosomes 77

Non-Arsenical Trypanocides

Pharmacology of Aromatic Diamidines 78

Metabolic Effects of Aromatic Diamidines 78

Biological Comparison of Bayer 7602(Ac) and a British Product 79

Sulphonamides

Local Action 79

Distribution in Tissues and Excreta 80

Sulphapyridine : Effect of Acid, Alkali, and Meals on Excretion 80

Sulphapyridine : Absorption through Human Pleura 81

Sulphonamide Dermatitis 81

Chemotherapy in Meningococcal Meningitis 81

Aspects of the Chemotherapy of Pneumonia 82

Effect of Chemotherapy on Mortality from Pneumonia 82

Sulphamezathine : Comparison with Sulphapyridine in Pneumonia 82

Sulphaguanidine : Neonatal Epidemic Gastro-Enteritis 82

Sulphaguanidine : Flexner Dysentery : Toxic Eruptions 83

Sulphadiazine : Staphylococcal Septicæmia 83

Sulphathiazole : Hæmatogenous Osteomyelitis 83

Sulphanilamide : Smallpox 84

Arsenical and Antimonial Compounds

Neoarsphenamine and Sulpharsphenamine : Biological Standardisation 84

Anthiomaline in Lymphogranuloma Inguinale 84

Some New Synthetic Drugs

Phemeride : A New Antiseptic Detergent 85

New Sarcopticides Compared 85

Promin in Pulmonary Tuberculosis 86

Routes of Administration : Local Reactions

Methods of Administration of Trypanocidal Drugs in Mice 86

Implantation of Non-Steroid Substances 86

Tissue Reactions to Implantation of Steroids 87

Acridine Antiseptics : Histological Effects 87

Proflavine Powder : Histological Effects 87

Sulphonamide-Proflavine Powder : Histological Effects 88

Mepacrine : Histological Effects of Intramuscular Injection 88

BOOKS, MEMORANDA, REPORTS 88

GUIDE TO THE JOURNALS 90

Dr. F. H. K. Green, who contributes the first article in this Number, is a member of the Administrative Staff of the Medical Research Council—a State organisation which, originally starting as the Medical Research Committee, received its present title and constitution in 1920. Dr. Green is Secretary of the Council's War Wounds Committee, and of some of its sub-committees, and also of the Therapeutic Trials Committee, the work of which is described in his article.

The author of the second article, Professor Warrington Yorke, whose death occurred on April 24th, 1943, was distinguished for his scientific and administrative work in association with the Liverpool School of Tropical Medicine. He had held the Alfred Jones chair of tropical medicine at Liverpool University since 1929, and had previously succeeded Sir Ronald Ross as Walter Myers professor of parasitology. He participated in expeditions to Africa to study blackwater fever (1907)

and sleeping sickness (1911, 1914). His scientific work covered a wide range of subjects in tropical medicine. In recent years his interest was especially centred on the chemotherapy of trypanosomal infections, and some of the fruits of this work are described in the article which is published in a revised form in this Number and which he wrote at the invitation of the British Council in 1942.

Dr. F. Hawking, who contributes the third and fourth articles, is a member of the Scientific Staff of the Medical Research Council, and has worked at the National Institute for Medical Research since 1940. He has published a number of papers on chemotherapy and on tropical medicine and pathology. Since the war, he has undertaken investigations on behalf of the War Wounds Committee and of the Malaria Committee of the Medical Research Council.

SPECIAL CONTRIBUTIONS

292

CLINICAL EVALUATION OF NEW REMEDIES IN BRITAIN

F. H. K. GREEN, M.D., F.R.C.P.

Administrative Staff, Medical Research Council

A problem necessarily confronting the manufacturers of a new drug is that of having it satisfactorily tested in patients, before it is placed upon the market. However encouraging the results obtained in pharmacological and toxicity tests in the laboratory, manufacturers of good repute will naturally be disinclined to offer a new product to the medical profession without previous evidence of its medicinal value and freedom from excessive toxicity in man, and without the authority of a published report upon its clinical action.

This problem has always been beset with greater difficulties in Britain than in some other countries, owing to a certain reluctance on the part of many British doctors to carry out clinical trials at the direct request of commercial firms, and especially to allow their names to be quoted as the authors of such tests. In some European countries, where there has been a closer liaison between the academic and commercial pharmacological laboratories, and between both these and university clinics, the problem does not arise. From the manufacturers' point of view, such a liaison has obvious practical advantages. Nevertheless, the clinical results published on this basis have occasionally been open to the uncharitable interpretation of an ulterior motive—especially where the clinical work is known to have been subsidised in greater or lesser degree by the interested commercial firm—and indeed it must be admitted that by no means all the reports on work done under these conditions have been of the highest scientific standing.

Space does not permit a discussion here of the ethical aspect of the attitude of many British doctors on this question, but it may be stated as an historical fact that the difficulty in securing direct clinical collaboration in regard to the testing of new remedies has in the past placed British manufacturers at a disadvantage compared with some of their European competitors.

Formation of a Therapeutic Trials Committee

These and other considerations led the *Medical Research Council*, after representations by the *Association of British Chemical Manufacturers*, to institute in 1931 an official scheme for the clinical testing of new remedies which in laboratory tests had given promise of therapeutic value. The *Council* appointed a Therapeutic Trials Committee of expert clinicians and pharmacologists, to advise in making the scheme effective and to act as a disinterested intermediary between the manufacturers and the medical profession in regard to the arrangement of the tests. From the beginning, it was agreed that new remedies of foreign as well as of British origin should be eligible for trial under the scheme. Naturally, also, it was decided that the arrangement should not be confined to the testing of products of commercial origin, but that new drugs prepared in academic laboratories should also come within its scope.

Conditions of Acceptance of New Remedies for Trial

Manufacturers applying to the *Medical Research Council* for clinical tests of their products must accept certain essential conditions for the investigations. First, the *Council* requires applicants to disclose "all such details as are necessary for the understanding of the true composition and nature of the remedy submitted for trial" and states that it will in no case accept any remedy for trial without full liberty to have the relevant scientific details of its composition disclosed in any report upon its clinical action which may ultimately be published; products of unrevealed composition are not accepted.

Secondly, having applied successfully for official clinical trials of a new product, the manufacturer has to undertake not to make any independent arrangement for its testing without the *Council's* permission. The main reason for this condition is, of course, to prevent the appearance of conflicting and confusing reports upon the product, due to the premature publication by independent workers of reports on its trial in inadequate series of cases, before the official investigation is complete. The effect of the requirement that independent trials shall not be undertaken is to exclude any product which has already been placed upon the market either in Britain or abroad. The purpose of this condition is that new remedies should be tested clinically *before* they are placed upon the market, as, on this basis, the manufacturer is saved the embarrassment of having to consider the withdrawal of his product from the market, in the event of unfavourable results of the tests. In applying for trials of his product, the manufacturer must indicate his acceptance of the conditions outlined above, and he is expected to provide such pharmacological and other laboratory data about the drug as make a *prima facie* case for its novelty and potential clinical value. An important principle governing the arrangement is that the *Council* is interested only in "new" substances, of which the therapeutic value has not been adequately explored: it is not willing to arrange tests of new brands or mixtures of well-known medicaments, however ingeniously these may have been compounded. The primary object is to promote new knowledge and discovery, and the clinical assessment, under controlled conditions, of entirely new types of therapeutic agents.

Organisation of Therapeutic Trials and Publication of Results

When the *Medical Research Council*—with the advice of its expert Committee—has accepted a remedy for trial, clinicians of high standing in the appropriate branches of medicine or surgery are invited to test it and to report to the *Council* on the results. Under the agreement with the manufacturers, the *Council* then has the right to decide whether it is in the public interest that the results—whether favourable or unfavourable to the remedy tested—shall be published, or whether they shall be communicated only to the manu-

facturer for his private information. When publication is decided upon, the usual practice is to authorise the clinician concerned to publish the results under his own name, in a suitable medical journal, as a *Report to the Therapeutic Trials Committee of the Medical Research Council*. This arrangement is of significance in relation to the points made in the opening paragraph of this article; as his findings are published with the authority of the *Council*, the clinician is clearly exonerated from any suspicion of special pleading on behalf of the products of the firm concerned; at the same time, as the report is published in his own name, he gets due credit for his work on the subject. When publication of a report on a drug is contemplated, the manufacturer is informed confidentially, in advance, of the results of the tests, on the understanding that he will make no public use of the information before the report appears. When the first official clinical report on a particular product has been published, the manufacturer is immediately at liberty to make such arrangements as he wishes for independent confirmatory trials or—if he thinks fit—to place the product upon the market. In marketing the product, he is entitled to refer in his trade literature to the official report.

For obvious reasons, it is generally considered desirable to arrange for the official clinical tests of a new remedy to be carried out at more than one hospital. The reports submitted from the various centres are then usually published simultaneously, or sometimes a conference of the clinical investigators is held, to collate their respective findings and to arrange the preparation of a joint report for publication. Experience has shown, however, that in occasional cases, where the product submitted for trial comes within the special field of interest of a well-established clinical research unit, time is saved by entrusting the official tests to research workers in the one unit, instead of distributing the product widely to clinicians throughout the country.

Practical Operation of the Scheme

Since the scheme was instituted in 1931, more than 40 new products have been accepted for official clinical trial, and reports on many of these have been published. Some of the investigations have been on a statistical basis, and these have been planned and assessed with advice from the statistical staff of the *Council*. In other cases, the notorious difficulty of securing controlled data in therapeutic research has been overcome by the organisation of "blind" tests, in which the effects of the product under trial have been checked by the administration on different occasions, or to different patients, of an inert substance of similar appearance. Not the least important aspect of the scheme is that in every instance where the results of the official clinical tests of a product have shown it to be unduly toxic or of little therapeutic value, and a report to this effect has been transmitted confidentially to the manufacturers, the latter have decided to withhold the drug from the market, or, at any rate, not to issue it for the purpose for which it was originally proposed.

It is not possible to list here the complete range of the official clinical tests of valuable remedies, but some outstanding examples may be given. Thus, the first large-scale trials of sulphonamido-crysoidin ("prontosil rubrum") in human streptococcal infections were carried out under the authority of the *Council* and published in reports to the Therapeutic Trials Committee (Colebrook & Kenny, 1936). These papers are generally regarded as "classical," as they established, in man, the therapeutic possibilities of the first sulphonamide drug, which, though discovered in Germany, had not there been taken much beyond the experimental stage. Some of the earliest controlled clinical tests of sulphanilamide were made under similar arrangements (Colebrook & Purdie, 1937; Snodgrass & Anderson, 1937). In another direction, clinical work done on behalf of the *Council* was responsible for establishing the therapeutic possibilities of the new group of synthetic oestrogenic agents, developed from the chemical researches of Dodds, Robinson and others in academic laboratories, of which stilboestrol (diethylstilboestrol) is the prototype: several synthetic oestrogens of this type have since been the subject of reports to the Therapeutic Trials Committee (Bishop, Boycott & Zuckerman, 1939; Winterton & MacGregor, 1939; Kellar & Sutherland, 1939; Bishop, Bowes, Boycott, Kellar, MacGregor & Murless, 1940; Barnes, 1942).

Complaints have sometimes been voiced by manufacturers that the official clinical tests carried out under the *Council's*

authority take an excessively long time to complete, as compared with tests made under private arrangements with doctors, where such are possible. Some manufacturers have also objected to the condition—laid down, it may be said, after consultation with the manufacturers' Association—that the makers of the product shall have no direct communication with the clinicians during the period of the tests; and it has been suggested that it is in the best interests of the investigation that the manufacturers should be kept in constant touch with its progress. While this, no doubt, is sometimes true, a relaxation of the condition, such as has been permitted in exceptional circumstances, does not always react to the benefit of the manufacturer, as the clinician's early impressions of a new drug are sometimes unduly favourable or unfavourable, and the manufacturer's assessment of the possibilities of his product on the basis of the preliminary clinical findings communicated to him may thus err on the side of optimism or of pessimism. Nevertheless, in the majority of cases, where communication between the manufacturer and the clinician is permitted only through the intermediary of the *Council*, an attempt is now made to keep the former informed as far as possible of important stages in the progress of the tests, and his advice is necessarily sought upon the question of any modification of the product which may seem desirable to increase its clinical usefulness.

Effect of War-time Conditions

During the war, the work of organising official tests of new remedies of general therapeutic interest has been restricted by a variety of circumstances, not the least of which is the difficulty of finding expert clinicians who have time and facilities to devote to the investigation of medicaments which have no specialised application to problems of war medicine. On the other hand, many clinical studies of new therapeutic agents of immediate importance in relation to current problems, such as the treatment of wounds, burns and various infective diseases, have been arranged. Outstanding among these are the clinical tests of penicillin now in progress under the authority of the *Council*, and the investigations organised by the War Wounds Committee of the *Council*, and its subcommittees, into the use of various bacteriostatic agents to control infection in wounds and burns. Clinical trials of British-made equivalents of several important pharmaceutical products of foreign origin have also been carried out. In relation to much of this *ad hoc* work, the manufacturers have been allowed to maintain closer contact with the clinicians making the tests than has hitherto been permitted in peace-time, and it is hoped that it will be possible to maintain this closer liaison on a satisfactory basis when the organisation of official clinical trials of new remedies is resumed on a full scale after the war. The *Council* also hopes to find a means of effecting a more intimate and sustained contact with the clinical centres where tests are made, so that the clinicians may be encouraged to complete their investigations, and report the results, with the minimum of delay.

Advantages of Organised Trials

So far as the writer is aware, the conclusions recorded in published reports to the Therapeutic Trials Committee regarding the practical value of therapeutic agents tested, have never been reversed in the light of later experience, though in one case—that of prostigmin—the investigations made for the Committee failed to reveal the full range of clinical utility of the product. Prostigmin was submitted to the *Medical Research Council* for trial in the relief of post-operative distention and paralytic ileus, and the published report to the Therapeutic Trials Committee (Carmichael, Fraser, McKelvey & Wilkie, 1934) dealt only with that aspect of its action; it was left to an independent investigator, who had noted from the official report that the drug was of relatively low toxicity compared with physostigmine, to discover that it also had a dramatic effect in myasthenia gravis.

It may reasonably be contended that the great majority of the published reports on clinical tests made under the authority of the *Medical Research Council* constitute substantial contributions to therapeutic research, and that the manufacturer whose product can be placed on the market with this official recommendation is in a much stronger position in issuing it commercially than if the tests had been arranged privately. Thus it may be maintained that, from the manufacturers' point of view, the reports upon the official clinical trials are usually well worth waiting for, even

though—owing to the wider scope of the inquiries—they sometimes take longer to appear than papers on tests carried out directly for the manufacturers by individual doctors.

The advantages of having an impartial body of medical experts to organise the clinical testing of promising new remedies of academic or commercial origin can hardly be denied, and it is to be hoped that with the post-war development of research in chemotherapy—which already, with the discovery of penicillin and related substances, holds prospects

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of such tremendous promise—the increasingly close co-operation of official, academic and commercial institutions in discovering new remedies and assessing their value, will lead rapidly to advances of far-reaching importance for medical practice throughout the world. Ultimately, of course, it must always be the doctor at the bedside who decides the clinical value of a new remedy, and it will be the aim of the *Medical Research Council* to ensure that he has every opportunity of doing so in the most effective and expeditious way.

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293

THE THERAPEUTIC ACTION OF THE AROMATIC DIAMIDINES IN THE TREATMENT OF PROTOZOAL INFECTIONS OF MAN AND STOCK *

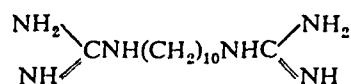
the late WARRINGTON YORKE, M.D., F.R.C.P., F.R.S.
Alfred Jones Professor of Tropical Medicine, University of Liverpool

In 1935, Jancsó & Jancsó in Hungary and Schern & Artagaveytia-Allende in South America, independently and almost at the same time, recorded that synthalin exerted a slight but definite therapeutic action in mice and rats infected with certain pathogenic trypanosomes. It has long been known that the pathogenic trypanosomes require an enormous amount of glucose for their metabolism, *vide* Yorke, Adams & Murgatroyd (1929), and the Jancsós concluded that the trypanocidal synthalin acts indirectly by producing a continuous hypoglycæmia which results in a "sugar-blockade" of the parasite metabolism. Schern & Artagaveytia-Allende reached a somewhat similar conclusion, but felt unable to exclude a possible toxic action of the drug on the parasites.

On consideration, it seemed so exceedingly improbable that any degree of hypoglycæmia compatible with the life of the host would suffice to affect its trypanosomal infections that I decided to re-examine the phenomenon. My colleague, Dr. E. M. Lourie, and I examined the trypanocidal action of synthalin *in vitro* by means of the technique described by Yorke, Adams & Murgatroyd (1929). We found that synthalin exerts *in vitro* a powerful trypanocidal action, which is of the same order as that of the aromatic trivalent arsenicals, a concentration of only 1 in 100 millions sufficing to destroy all the trypanosomes in a suspension of nutrient medium within 24 hours at 37° C. Furthermore, we satisfied ourselves that synthalin does not produce any pronounced degree of hypoglycæmia in the normal animal given in doses which produce serious damage to the liver, and finally, that insulin exerts no trypanocidal activity either *in vivo* or *in vitro*.

From this work, Lourie & Yorke (1937) concluded that the therapeutic action of synthalin does not depend upon any hypoglycæmia which it may produce, but upon its direct lethal effect on the parasite. This discovery that the trypanocidal action of synthalin is a direct one opened a wide field of biological and chemical inquiry. It was, moreover, of considerable interest in that the chemical constitution of synthalin is essentially different from that of all known trypanocidal

substances. As the following formula shows, synthalin consists of two guanidine groups connected by a long alkylene chain:

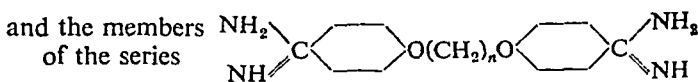
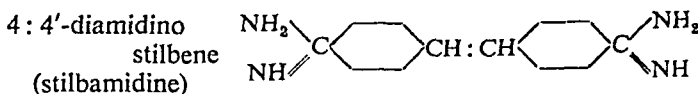


With the collaboration of Dr. H. King of the *National Institute of Medical Research*, London, a large number of guanidines, isothioureas, amidines and amines with alkyl and alkylene chains were prepared and examined for trypanocidal activity.

Chemotherapeutic Investigation of Diamidines

It was found that certain of the diamidines exhibited a powerful trypanocidal action both *in vivo* and *in vitro*, and that with the most active member of the series, viz., undecane-1:11-diamidine, it was possible to produce permanent cures in approximately 100% of mice and rabbits infected with our laboratory strain of *Trypanosoma rhodesiense*.

Immediately following the publication of this work (King, Lourie & Yorke, 1937; 1938) Dr. A. J. Ewins of the firm of May & Baker took up the investigation of a series of aromatic compounds containing the amidine group. Examination of these compounds showed that many of them exhibited considerable trypanocidal activity, and that some of them did so in a quite remarkable degree. The most active of Ewins' compounds were found to be:



viz., 4:4'-diamidino diphenoxypropane (propamidine),¹ where $n = 3$.

4:4'-diamidino diphenoxypentane (pentamidine), where $n = 5$.

Each of these compounds is tolerated by mice when administered intraperitoneally in doses up to 1 mg. per 20 g. mouse. Diamidino stilbene is slightly more active than the others. Such minute doses as 0.005 and 0.00625 mg. per 20 g. mouse suffice to clear the peripheral blood in more than 50% of mice infected with our strain of *T. rhodesiense*; permanent cures are sometimes obtained with doses of 0.01

* [This paper was contributed, at the invitation of the British Council, in 1942. It was translated into Spanish and submitted for exclusive publication in Argentina (*Prensa méd. argent.* 29, 1679-87). As an authoritative review of the development of work on an important new series of compounds, it has been considered to be of sufficient interest for republication in *BMB*. The article has been revised and minor alterations and omissions have been made. In addition, the *Bureau of Hygiene and Tropical Diseases* has kindly provided references to the later literature, which have been interposed in the text in square brackets. These changes have been made in the interest of conformity with later findings, but the article remains essentially as originally written.]

¹ [This compound has also been found effective as a wound antiseptic (*see BMB* 58).]

and 0.0125 mg., and with doses of 0.025 and 0.05 mg. the great majority of the animals are permanently cured. The therapeutic index $\left(\frac{\text{maximum tolerated dose}}{\text{minimum curative dose}} \right)$ of diamidino stilbene is therefore about 30. Experiments on rabbits infected with *T. rhodesiense* gave equally satisfactory results. The maximum dose of diamidino stilbene tolerated by rabbits when administered intravenously is about 20 mg. per kg. of body weight. A dose of 0.5 mg. per kg., i.e., $\frac{1}{40}$ th of the maximum tolerated dose, repeated on each of 5 consecutive days, sufficed to produce permanent cures in all the cases, even though at the time of commencement of treatment the rabbits had been infected between 3 and 4 weeks and exhibited pronounced lesions.

In view of the remarkable activity displayed by certain of the aromatic diamidines on *Trypanosoma rhodesiense* infections of laboratory animals, it appeared to be of interest to ascertain whether they exerted any therapeutic activity in other protozoal or in spirochaetal infections. For this purpose, the following were selected: *Trypanosoma equinum*, *T. congolense* and *T. cruzi*; *Spirochaeta recurrentis* and *Spirillum minus*; *Plasmodium relictum* of canaries, *P. knowlesi* of monkeys, and the malaria parasites of man; *Babesia canis* in puppies; and *Leishmania* infections in hamsters.

The results of this work (Lourie & Yorke, 1939a; 1939b) can be briefly summarized as follows:

T. equinum infections of mice appear to be just as susceptible to the diamidines as are *T. rhodesiense* infections.

T. congolense infections of mice: Most of the compounds tested displayed some action on these infections, but cures were obtained only with diamidino stilbene: all of seven mice were cured by a single maximum dose of 1 mg. of this compound, and all of eight mice were cured by 0.25 mg. given on each of three consecutive days. Recently it has been found (Fulton & Yorke, 1942a) that a closely allied diamidine, viz., 4:4'-diamidino dimethyl stilbene, is considerably more active in this infection, mice being cured by a fourth or less of the tolerated dose.

T. cruzi infections of mice: The compounds tested had no action on this infection.

Spirochaeta recurrentis and *Spirillum minus* infections of mice were uninfluenced by these compounds. In this connection it is interesting to note that Dr. Lourie, writing from Sierra Leone, British West Africa, reported that diamidino stilbene had no action on yaws (framboesiasis).

Plasmodium knowlesi of monkeys and *P. relictum* of canaries: diamidino stilbene and diamidino diphenoxypentane were tested by Dr. J. D. Fulton (1940) on these infections; both were found to exert a definite therapeutic activity on the monkey malaria infection, and the latter compound also exerted some influence on the canary infection.

Malaria in man: Diamidino stilbene was found to exert a definite action on induced *P. vivax* infections in patients with dementia paralytica, but little or no action on natural infections with *P. falciparum*.

Babesia canis in puppies: Since Nuttall (1909) drew attention to the therapeutic activity of trypan blue in babesia infections, many attempts have been made to find a more efficient remedy. Apart, however, from the discovery of Stephan & Esquibel (1929) that acriflavine also exerted a definite action on certain babesia infections, there seems to have been no real advance in the therapy of this important group of diseases until 1935, when Kikuth and others published accounts of very successful results obtained with a Bayer product known as acaprin—6:6' (di-N-methyl-quinolinium-methosulphate) urea—in the treatment of various babesia infections.

In our experiments we used a strain of *Babesia canis* obtained from Kikuth, of Elberfeld; this strain is very virulent for young puppies, killing them usually in from 4 to 6 days. We found that most of the aromatic diamidines examined had a definite action on the infection in that they caused the parasites to disappear from the blood for a time. The most active compounds were diamidino stilbene (4:4'-R-CH:CH-R), diamidino diphenyl ether (4:4'-R-O-R), and diamidino diphenoxypropane (4:4'-R-O(CH₂)₃-O-R). Single large doses of these compounds or two smaller doses given on successive days sufficed to sterilize the infection.

Leishmania infections in hamsters [*Cricetus auratus*]: A quantity of diamidino stilbene was sent to Professor S. Adler, of Jerusalem, with the request that he would test the substance

in hamsters infected with *L. donovani*. In due course, Adler reported that this compound had a marked therapeutic action on infections of *L. donovani* in the Syrian hamster. In the three animals sufficiently studied, the infection was sterilized by 27 injections of 2.5 mg. per kg. of body weight, 24 injections of 10 mg. per kg., and 10 injections of 20 mg. per kg. As Adler points out, this observation is of great interest as it is the first instance of a drug not containing antimony with a therapeutic action on infections of *L. donovani*.

Summarizing all this experimental work, we find that certain of these aromatic diamidines exert a powerful curative action on *Trypanosoma rhodesiense* and *T. equinum* infections, on *Babesia canis* infections and on *Leishmania donovani* infections, that they exert a less powerful action on *T. congolense* infections and on certain malaria infections of man and monkeys, but that they have no effect on *T. cruzi* infections or on those due to *Spirochaeta recurrentis* or *Spirillum minus*.

Clinical Tests

Since 1939, certain of these compounds have been tried clinically on man suffering from African sleeping sickness and from leishmaniasis, respectively, and also on domesticated animals infected with *Babesia*. The results of these clinical trials which have so far been received are summarized below.

African Trypanosomiasis

The therapeutic action of diamidino stilbene on patients suffering from sleeping sickness has been examined by McLetchie (1940) and by Harding (1940) in Northern Nigeria, and by Bowesman (1940) in the Gambia, while Saunders (1941) tested diamidino diphenoxypentane in the Gold Coast.

[During 1939–41 Lourie (1942) treated cases of *T. gambiense* infections in Sierra Leone with diamidino diphenoxypentane, diamidino diphenoxypropane and diamidino stilbene. In early cases the two former drugs are almost as effective as antrypol or tryparsamide, and have the distinct advantage that the course of treatment is completed in much shorter time. Diamidino stilbene is considerably less valuable. In late cases tryparsamide is much more effective than the diamidines. Immediate but transient toxic effects were noted, but no late ill-effects occurred; the maximum doses given were 100 mg. daily for 12 days. The author remarks that other workers, using heavier doses, have reported severe delayed toxic effects on the liver, and refers to the neuropathies reported from India (see below).

Lawson (1942) treated 53 cases of *T. gambiense* infection in Uganda by 10 daily intravenous injections of 0.1 g. diamidino diphenoxypentane (for adults). He reports rapid sterilization of the blood, and considers this to be probably the best drug so far introduced for the treatment of early cases with low cerebrospinal fluid cell count. For those with higher counts he advocates a pentavalent arsenical.

Gilbert (1943), from observations on a small series of cases of *T. gambiense* infection, advocates doses of at least 2.0 mg. per kg. body weight, preferably given intravenously, in two courses of 8 injections each, separated by an interval of one week.]

From all this work the following provisional conclusions seem permissible:

i. The diamidines are powerfully trypanocidal substances and quickly cause peripheral sterilization.

ii. Early cases with normal cerebrospinal fluid are apparently cured by a short course of any of the three diamidines.

iii. As regards the action of these compounds on late cases of *Trypanosoma gambiense* infection, it appears that diamidino stilbene and the other diamidine compounds fail to cure these cases. Lourie's preliminary reports suggest that diamidino diphenoxypentane and diamidino diphenoxypropane may prove more valuable than diamidino stilbene.

Human Leishmaniasis

Indian kala-azar: The first human case of this disease treated with one of the aromatic diamidines was that reported upon by Adams & Yorke (1939). The patient, a Hindoo, was exceedingly ill, much emaciated, anæmic, with a spleen reaching the umbilicus and fever of a remittent type; *Leishmania donovani* was found in bone-marrow smears and cultures of the blood were positive. He was given diamidino stilbene intravenously in doses of 1.0 mg. per kg. daily for

8 consecutive days. A few days after the end of treatment, the temperature became normal and the spleen commenced to shrink rapidly. By the 17th day after treatment the spleen was just palpable below the costal margin, and the size of the liver had decreased coincidentally with that of the spleen. When the patient was discharged from hospital 2½ months after treatment, he appeared to be perfectly well. His weight had increased by 4 kg., cultures of the blood and bone-marrow smears were negative, and the anaemia and leucopenia had practically disappeared.

Subsequently, a second case of Indian kala-azar was successfully treated by Adams & Yorke (1940) with a similar course of diamidino stilbene; and later Wingfield (1941) recorded details of another case also apparently cured by a short course of this drug.

Napier & Sen (1940) tested diamidino stilbene in the Calcutta School of Tropical Medicine. They treated a series of 8 cases of Indian kala-azar, all of whom were apparently cured by a course of 8 to 12 daily injections of 1 to 2 mg. per kg.

Adams (1941) tried diamidino diphenoxypentane in a case of Indian kala-azar; the patient was apparently cured by a course of 8 daily injections, each consisting of 1 mg. per kg.

[Napier, Sen Gupta & Sen (1942) have reported on 100 cases of Indian kala-azar treated with diamidino stilbene in doses up to a maximum of 1 mg. per pound [about 0.45 kg.] of body weight. Reactions were troublesome but apparently free from danger; the fall in blood pressure could be prevented by an injection of 0.25 cm.³ of 0.1% adrenaline just before administration of the drug. Of these patients 2 died, and 98 were cured except that in 2 there were relapses. The authors state that the introduction of stilbamidine has made a great advance in the treatment of kala-azar; antimony-resistant cases respond well.

Napier & Sen Gupta (1943) have used pentamidine in doses up to a maximum of 1 mg. per pound body weight for Indian kala-azar, with satisfactory results, but Napier, in an editorial in the same journal, sums up the position in the sense that the majority of Indian patients will continue to be treated with antimonials, the diamidines being reserved for antimony-resistant cases.]

Mediterranean and Sudan leishmaniasis: Adler & Rachmilewitz (1939) tried diamidino stilbene on a woman infected with *Leishmania infantum*. The patient, who had contracted the disease in Palestine, had relapsed after a course of stiburamine. Between July 5th and September 7th, 1939, the patient was given a series of 24 injections of diamidino stilbene, the individual doses varying from 1.0 to 1.7 mg. per kg. When the patient was discharged on October 8th, she had increased in weight and appeared to be in excellent condition. The authors write that in view of the clinical severity of the case, the size and hardness of the spleen and, above all, the fact that they were dealing with a relapse case, the result must be regarded as satisfactory.

In a letter dated July, 1941, Adler mentioned that he had successfully treated with diamidino stilbene a second case infected with *Leishmania infantum*. The patient, a child, was desperately ill. In all, she was given about 90 injections, the individual doses ranging up to 2.5 mg. per kg. Adler reported that the child had been quite well for some months and he believed that she was cured.

Kirk & Sati (1940) examined the therapeutic activity of the aromatic diamidines on a large scale in the field. These workers treated a series of 43 cases of Sudan leishmaniasis—28 with diamidino stilbene, 13 with diamidino diphenoxypentane, and 2 with diamidino diphenoxypentane.

Among the 28 cases treated with diamidino stilbene, there were 4 deaths and 24 recoveries, giving an immediate recovery rate of 86%. Of the 24 immediate cures, 6 cases had at the time of the report been under observation for a period of 6 to 7 months, during which there had been no relapse. Of the 4 fatal cases, 3 were moribund when treatment commenced and died when they had received only 3, 4 and 5 doses, respectively; the fourth was a child of four who appeared to be progressing well but died suddenly from unknown cause on the day following the seventh injection. Among the 13 cases treated with diamidino diphenoxypentane there were 3 deaths, 9 immediate recoveries and one doubtful recovery. Of the 3 fatal cases, one had lobar pneumonia when admitted and was moribund; one appeared to be making an excellent recovery, but after being afebrile for three weeks went out and drank a great deal of native beer, returning to hospital very intoxicated and dying 48 hours

later; and in the third the condition was complicated by nephritis and severe diarrhoea which resisted every form of treatment. Of two cases treated with diamidino diphenoxypentane, one (who also had pneumonia) recovered, but the other, a man of 30 who on admission was in an extremely dirty, verminous and exhausted condition and weighed only 5 stones [about 32 kg.], died after the fourth injection.

In addition to these cases, Kirk & Sati refer briefly to three antimony-resistant and antimony-relapsed cases who were provisionally cured by diamidino stilbene, and also to two cases of *espundia* who were discharged as possible cures after treatment with diamidino stilbene. Lastly, Kirk & MacDonald (1940) give details of an interesting case of Sudanese leishmaniasis who had relapsed after treatment with neostibosan. This patient exhibited peripheral neuritis—presumably the result of previous antimony treatment—a conspicuous nodular depigmented eruption on the face, a minutely punctate rash over the rest of the body, and muco-cutaneous lesions at the orifice of the nose and on the nasal septum. The patient, who was given a course of diamidino diphenoxypentane, was discharged as cured.

Apparently, then, Kirk and his collaborators tried the various diamidines on a total of 49 cases of Sudan leishmaniasis, 41 of whom were provisionally cured. Of the 8 fatal cases, 5 were moribund when admitted and died after only 3 to 5 injections. If we omit these 5 moribund cases and the patient who broke out of hospital and died after a debauch, there remain 43 cases, 41 (95%) of whom were provisionally cured.

Colonel Hamilton Fairley in a letter dated December, 1941, stated that most satisfactory results were obtained with diamidino stilbene in over 30 cases of Sudan leishmaniasis occurring among British troops.

As Kirk & Sati point out, these results compare most favourably with those hitherto obtained in the treatment of Sudan leishmaniasis with the antimonials. They write:

"The clinical picture of the uncomplicated disease is a grave one. Intractable diarrhoea, hæmorrhages, and complications like cancrum oris and lobar pneumonia are frequent. Experience with antimony has shown that the Indian standard treatment is inadequate in the Sudan disease, where the action of the drug is much slower. A larger total dose is usually required to effect a cure, and cases are frequently encountered which are completely resistant to any form of antimony treatment. Moreover, Sudanese kala-azar patients are very sensitive to the toxic effects of antimony, and the early attempts to treat the Sudan disease with this drug along the lines advocated in India led only to a series of disasters, which Archibald recognized as attributable to the drug rather than to the disease."

In view of the relatively great difficulty which has been experienced in curing Mediterranean and Sudan leishmaniasis with antimonials, it is not surprising that both Adler & Kirk found that much larger quantities of the diamidines were required in this form of leishmaniasis than in Indian kala-azar. The size of the individual dose given varied between 1.0 and 2.5 mg. per kg., and apparently at least 30 injections were necessary to produce a cure.

[Diamidino diphenoxypentane was tried in a case of kala-azar in Liverpool (Adams, 1943). Intravenous administration of 100 mg. daily for 9 days elicited a good response, although there was local reaction at the site of infection.]

From this work it seems possible to draw the following provisional conclusions:

- i. Indian kala-azar can be cured with a short course consisting of 8 to 12 injections of 1 mg. per kg. of diamidino stilbene or diamidino diphenoxypentane.

- ii. The great majority of cases of Mediterranean and Sudan leishmaniasis can be cured by these diamidines, but a much longer course is required than is the case with Indian kala-azar. The results obtained with the diamidines appear to be considerably better than those hitherto obtained with the antimonials.

[Süsskind & Roth (1943) have treated one child with Mediterranean kala-azar with two courses of stilbamidine, one consisting of 38 injections, the other of 87. The result was satisfactory. The drug was given daily for part of the time, but in other parts of the course there were intervals of 1 or more days between injections.]

Field Tests in Animals

Babesiosis in Domesticated Animals

In view of the successful results obtained by Lourie & Yorke (1939b) in the treatment of puppies experimentally

infected with *Babesia canis* by diamidino stilbene, diamidino diphenyl ether and diamidino diphenoxypropane respectively, it was decided to ask Professor Adler to test these compounds in animals infected with various piroplasms in Palestine.

Adler & Tchernomoretz (1940) examined the effect of diamidino stilbene on the following: *Theileria annulata* in calves, *Anaplasma marginale* in calves, *Anaplasma ovis* in goats, *Babesiella ovis* in goats and *Babesia bigemina* in calves. They found that the drug had no effect on *Theileria annulata* infections, nor on the *Anaplasma* infections in splenectomized calves and goats. On *Babesiella ovis* infections in goats and *Babesia bigemina* in calves, however, the drug had a very marked therapeutic action. In order to exclude the natural defences against the parasites, Adler and Tchernomoretz used only splenectomized animals. They found that in doses of from 2 mg. to 4 mg. per kg. diamidino stilbene is effective in the treatment of *Babesiella ovis* in goats and *Babesia bigemina* in calves, and that the action of the drug in the latter infection is very rapid.

Daubney & Hudson (1941) examined the therapeutic action of diamidino stilbene on 16 dogs naturally infected with *Babesia canis* in Kenya. Most of the animals were pure bred, very often the progeny of imported parents, and the majority of the attacks were primary infections in animals ranging from a few weeks to 12 months old. In 15 of the dogs the dose employed was 1.5 mg. per kg. given subcutaneously. In 13 there was rapid clinical recovery, the blood was negative within 48 hours, and there was no relapse; two advanced cases—one of which was moribund when treated—died. The sixteenth animal was given 0.9 mg. per kg. Here also the blood was negative within 48 hours, but a relapse occurred 4 days later.

Daubney & Hudson also record the result of treating with diamidino stilbene two cases of biliary fever (*Babesia caballi*) in horses. One of these animals was a foal and the other a thoroughbred horse. Both made a rapid recovery and no relapse was observed.

Daubney & Hudson draw attention to certain transient toxic effects in dogs. Within a few minutes most of the animals showed evidence of hyperæsthesia, and in more than half of them there was transient swelling of the face. Two animals appeared to have some difficulty in breathing, and some attempted to vomit. After about 20 minutes, these untoward effects passed away and the animals settled down to sleep; the next day they were much brighter than before treatment and from then onwards recovery was uninterrupted.

The two horses treated with diamidino stilbene also exhibited transient toxic signs. The foal showed signs of hyperæsthesia similar to those seen in dogs, with swelling of the muzzle and tongue. These symptoms passed off within a few hours. The thoroughbred horse was apparently greatly distressed for about 48 hours after the injection, sweating profusely and behaving as though suffering from violent colic. When these symptoms subsided, the animal made a rapid recovery. A third uninfected horse showed similar signs.

Daubney & Hudson conclude that diamidino stilbene is a useful therapeutic agent in the treatment of clinical cases of tick fever in dogs, but that the drug is unsuitable for administration to horses, notwithstanding its efficacy in the cure of biliary fever.

Carmichael & Fiennes (1941) tested another of these compounds, viz., diamidino diphenoxypropane, in dogs naturally infected with *Babesia canis* in Uganda: The dosage used was that recommended by Lourie & Yorke (1939b), i.e., either a single dose of 5 mg. per kg., or a dose of 2.5 mg. per kg. on each of two consecutive days. Subcutaneous, intravenous and intramuscular routes proved equally effective, but the intramuscular route was preferred, as when the subcutaneous route is used, an œdematous swelling may result and persist for a month or six weeks. The dogs brought for treatment included animals in all stages of the infection, from those at the beginning of the disease to those which had been sick for some time and were nearly moribund. Of the 116 animals treated, 102 were definitely cured by the single dose of 5 mg. per kg. or by the two smaller doses given on consecutive days; 10 relapsed but were cured by a second dose, and 4 died. No signs of toxicity were detected. The authors contrast their results with those previously obtained by Carmichael (1935) with trypan blue and with acaprin, and conclude that diamidino diphenoxypropane has proved the most valuable drug they have so far encountered in the treatment of tick fever in dogs.

Carmichael has also examined the action on dogs naturally infected with *Babesia canis* in Uganda of another of the diamidines found by Lourie & Yorke to be effective in this infection, viz., diamidino diphenyl ether. In a cable dated the 18th August, 1941, Carmichael said that 20 cases were very successfully treated, without death or relapse, by a subcutaneous injection of 10 mg. of the compound per kg.

The general conclusion from this work appears to be that diamidino stilbene, diamidino diphenoxypropane and diamidino diphenyl ether are of practical value in the treatment of babesiasis in the field. The last two compounds are probably of most value in the treatment of dogs because they are definitely less toxic for these animals than is diamidino stilbene. There is, as yet, not sufficient evidence to state which of these compounds is preferable for the treatment of horses, cattle, sheep and goats. Adler's work indicates that the diamidines have no action in infections due to *Theileria* and *Anaplasma*.

Toxicity

Acute. The aromatic diamidines have now been administered to some hundreds of human beings. They have been given both intravenously and intramuscularly. Owing to their great solubility, diamidino diphenoxypropane and diamidino diphenoxypentane are more suitable for intramuscular injection into man and the larger animals than is the less soluble diamidino stilbene. The normal dose has been 0.5 to 2.0 mg. per kg.

No serious example of acute toxicity has so far been reported, but many of the patients who received the larger doses (1.0 and 2.0 mg. per kg.) by the intravenous route have exhibited transient symptoms. As a rule, these were slight, and varied from flushing of the face and indefinite epigastric sensation to headache, dizziness, rapid pulse, sweating, retching and, rarely, vomiting. All these effects disappeared within half an hour. Occasionally, however, intravenous injections have been followed by more alarming symptoms—syncopal attacks with temporary loss of consciousness and epileptiform twitching; these symptoms also were very transient and disappeared in a few minutes.

It would appear that most, if not all, of these immediate disagreeable effects are connected with the dramatic fall in blood pressure which follows intravenous injection of the diamidines. Adams (1941) observed that within a minute of the intravenous injection of 1 mg. per kg. of diamidino diphenoxypentane the systolic pressure fell from 106 to 50 and that it had returned to normal within 10 minutes. After a similar dose, given intramuscularly, the systolic pressure fell from 106 to 80 within 3 minutes; after 10 minutes it had increased to 95, and thereafter slowly returned to normal. These observations correspond with the fact that the undesirable transient symptoms are less marked after intramuscular than after intravenous injection.

[The pharmacological properties of the diamidines have more recently been studied by Wien (1943) and by Wien, Freeman & Scotcher (1943). The compounds have a depressant action on the circulatory system, but the fall in blood pressure may be reduced or prevented by a previous injection of calcium.]

Chronic. Albuminuria and other signs of renal irritation have not been observed. Information received from the Sudan in 1942 indicated that the diamidines possessed cumulative action, and that prolonged administration of large doses might produce serious damage to the liver. A certain number of cases of Sudan kala-azar received the following doses of diamidino stilbene: first week, 2 mg. per kg. daily; second week, 3 mg. per kg. daily; third week, 4 mg. per kg. daily. In these cases the cure of the kala-azar was apparently very rapid, and the patients were discharged from hospital a short time after completion of the treatment. However, a few weeks later a number of these patients presented signs of serious hepatic insufficiency, and some of them died.

It seems clear that the diamidines should be employed with caution, that the daily dose should probably not exceed 1 to 2 mg. per kg., and that the treatment should be interrupted after a week or 10 days. With the object of protecting the liver Adler recommends simultaneous administration of large doses of glucose and calcium.

[Kirk made the suggestion that solutions of diamidino stilbene which had been kept for some time increased in toxicity. Fulton & Yorke (1942b) investigated the matter and

noted that solutions of diamidino stilbene, though unchanged by heating for short periods and by storage for 14 days in the dark, are rendered considerably more toxic by relatively short exposure to daylight. Fulton (1943) found that other of the unsaturated compounds were similarly affected, and the practical application of this work is that solutions of the unsaturated amidines should be freshly prepared for use. Barber, Slack & Wien (1943) arrived at similar conclusions, and Henry (1943) has extended the observations on the toxic products of exposure to light, with a view to finding stable compounds. In the paper quoted above, Fulton & Yorke note that late toxic symptoms in Sudanese patients developed some time

after the completion of the course of treatment for kala-azar, and suggested toxic degeneration of the liver, and possibly of other organs, resulting from a cumulative toxic action. These drugs are known to cause fatty degeneration of the liver in dogs and cattle, and peculiar nervous symptoms have been produced in dogs.

Napier & Sen Gupta (1942), and Sen Gupta (1943) have noted a neuropathic sequel of diamidino stilbene therapy, in which, 3-4 months after completion of treatment, there were sensory disturbances over the area supplied by the trigeminal nerve. This is probably due to toxic degeneration of the nerve, but tends towards slow recovery.]

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¹ [see BMB 315]

² [see BMB 316]

RECENT WORK ON THE PHARMACOLOGY OF SULPHONAMIDES

FRANK HAWKING, D.M.

National Institute for Medical Research, London

Under the heading of pharmacology, it is convenient to consider all the actions of sulphonamide compounds on the body of the host, excluding the detailed discussion of the toxic symptoms encountered in clinical practice. On the whole, sulphonamides are rather inert from a pharmacological standpoint, and the greater part of any article on this aspect is necessarily occupied by a consideration of the factors involved in maintaining an optimal concentration at their site of action.

Methods of Estimation

The study of blood concentrations has been a special feature of the history of sulphonamides. Although methods of estimation were described at an earlier date by Fuller (1937) it is to Marshall and his school that we owe this special development, which has had most fruitful consequences. Numerous papers have appeared during recent years, but few of them contain anything new. Difficulties in the estimation of sulphathiazole are discussed by Sunderman & Pepper (1940). A simple rapid method using tablets of reagents and a wedge of coloured lucite to match the colour is reported by Sheftel

(1941). The estimation in bile is described by Carryer & Osterberg (1942), the bile pigments being precipitated by zinc sulphate and potassium carbonate. Methods of micro-estimation are given by Churg & Lehr (1941), Jorgensen (1942) and Lee, Hannay & Hand (1943). Microtests, using a strip of paper impregnated with Ehrlich's reagent (*p*-dimethyl-aminobenzaldehyde in acid), have been described for blood (suitable for use at the bedside) by Fuller (1942), and for serum by La Rosa (1943). Bogen (1943) reports a simple method of testing urine to see if the patient has already received sulphonamide (a drop of urine is placed on wood-pulp paper, e.g. newspaper, and a drop of hydrochloric acid is added; with sulphonamide a yellow colour appears). A method for histological demonstration in the tissues is given by MacKee, Herrmann, Baer & Sulzberger (1943). Procaine (novocaine) gives the same colour as sulphonamides in Marshall's test (which can thus be used for its estimation); consequently this and other local anaesthetics which contain the *p*-aminobenzoate group must not be used for the collection of specimens for sulphonamide estimations (Butler & Nadler, 1941).

Absorption

When sulphonamides are taken by mouth they are rapidly absorbed. Apparently most of this absorption occurs in the upper part of the small intestine, but there is evidence suggesting that much may be absorbed through the stomach wall. Usually absorption is complete before the ileocaecal valve is reached. Sulphanilamide and sulphathiazole are rapidly absorbed, sulphadiazine more slowly. The absorption of sulphapyridine is slower, less regular, and less complete than that of the other compounds (Kinsman, Moore & Harrison, 1940). Absorption from the large intestine can occur, but the rate is slower (Turell, Marino & Nerb, 1940; Marshall, Bratton, White & Litchfield, 1940). In cases where oral administration is not possible, e.g. after operation on the stomach, sulphanilamide may be given per rectum, but the amount absorbed is always uncertain and the resulting blood levels tend to be low (Wood, 1941). Sulphapyridine and sulphadiazine are both poorly absorbed from the large intestine (Peterson, Strauss, Taylor & Finland, 1941).

If the sulphonamide is given with an empty stomach, it is absorbed slightly more quickly than if given after a meal; but the difference is not sufficiently great to be of clinical importance or to compensate for the greater risk of nausea. Similarly the administration of acid or alkali at the same time as the sulphonamide does not appreciably alter the rate of absorption (Peterson & Finland, 1942; Wilson, 1943). When sulphapyridine, sulphathiazole or sulphadiazine are given by tube directly into the duodenum, absorption may be greatly diminished, suggesting that a considerable portion of the sulphonamide may reach the blood stream through the stomach wall; this effect was not shown when sulphanilamide or sodium sulphadiazine were given (Peterson & Finland, 1942). When very rapid absorption is required, as in meningitis, it has been suggested (Loughlin, Bennett, Flanagan & Spitz, 1943) that the sodium salt of sulphadiazine (or sulphathiazole) might be given while the stomach is empty, but the issue of the sodium sulphonamides for oral administration has not received the approval of the *Council on Pharmacy and Chemistry* of the American Medical Association, and in such cases it is better to inject the compound intravenously (or intramuscularly). It is claimed that the absorption of sulphanilamide can be accelerated by giving it as a solution with glucose, glycerin and sodium lactate, or with sodium lactate and potassium citrate, but the difference is not great enough to be of clinical value (Siebert & Loose, 1940).

Sulphanilamide and the soluble preparations of the other sulphonamides are quickly absorbed when injected intramuscularly or subcutaneously. Absorption is of course most rapid (instantaneous) when the compound is injected intravenously. Absorption is also rapid from serous cavities, such as the peritoneum and pleura (Hawking & Hunt, 1942; Vickers, 1943), from large raw areas, e.g. burns, and from large wounds (depending on their size, shape and vascularity); on the average absorption from these sites is about half as rapid as from the alimentary canal.

Distribution

After absorption into the blood stream, sulphanilamide diffuses through the whole body. In dogs, about 4 hours after an oral dose, the compound is distributed approximately evenly through all the tissues except bone and fat, and the concentration in the tissues is equal to that in the blood (Marshall, Emerson & Cutting, 1937b). During the period preceding this phase of equilibrium, the concentration in the blood is greater than that in the tissues; following this phase, the blood concentration is lower than the tissue concentration (Alexander, 1943). Although there is no tendency for the compound to be concentrated in any special tissue, some organs contain more than others. Thus during the first six hours (in rabbits) if the concentration in the blood is taken as 1.0, the average concentration in the liver is 1.2, in the kidney 2.0-3.6, in the brain about 0.6, and in the muscle 0.8 (Alexander, 1943). According to some figures of Waterhouse & Shannon (1942) for dogs, if the concentration of sulphanilamide in the plasma is taken as 1.0, that in the erythrocytes is 1.4, in the lung 1.1, in the liver 1.3, in the pancreas 1.1, in muscle 1.1, in the cerebrospinal fluid and in the brain 0.6, and in nerves 0.76. In dogs, no acetylation occurs and all the sulphanilamide is present in the free form. Some figures for the distribution of sulphapyridine in the organs of patients dying of meningitis are given by Janbon, Chaplat & Lazerges (1942).

The distribution in the blood between the erythrocytes and the plasma differs somewhat with the different compounds. Thus if the concentration of the free form in the plasma is 1.0, that in the erythrocytes is:

sulphanilamide	1.0-2.1	{ (Simesen, 1941a, 1941b; Reinhold, Flippin, Schwartz & Domm, 1941; Ratish, Shackman & Bullowa, 1942; Murphy, Clark & Flippin, 1943)
sulphapyridine	0.6-1.1	
sulphathiazole	0.3-0.4	
sulphadiazine	0.25-0.5	
sulphamerazine	0.3	
sulphacetamide	1.5	
uliron	1.0	

Similarly as regards the penetration into the cerebrospinal fluid, if the concentration in the plasma is 1.0, that in the cerebrospinal fluid (when equilibrium is reached) is:

sulphanilamide	0.7-1.0	{ (Marshall & Litchfield, 1939; Sadusk, Blake & Seymour, 1940; Banks, 1941; Long, 1941; Reinhold, Flippin, Schwartz & Domm, 1941)
sulphapyridine	0.7	
sulphathiazole	0.15-0.4	
sulphadiazine	0.5-0.8	
sulphamezathine	0.5-0.8	(Macartney, Smith, Luxton, Ramsay & Goldman, 1942)
sulphamerazine	0.3-0.7	(Murphy, Clark & Flippin, 1943)

(Probably the differences between the various compounds are due to the differing amounts "bound" to the plasma proteins; see below). Actually the ratio (concentration in C.S.F./concentration in plasma) is lower than these figures during the earlier part of treatment, when the blood concentration is rising, and higher when administration of the drug is stopped and the blood concentration falls. Similarly, the concentration in peritoneal, pleural and joint effusions, tends to be somewhat lower than that in plasma when equilibrium is reached; but there is a lag of 2-3 hours in arriving at this position (Cantarow, Cubberley & Rakoff, 1942). Prontosil rubrum enters the cerebrospinal fluid only with difficulty, but prontosil soluble enters more easily (Katzenelbogen, Cruvant & Silverberg, 1941). The concentration of sulphathiazole in the fluid of infected or uninfected knee joints is approximately the same as that in the blood (Heyl, 1941). As regards the eyes, when sulphanilamide is given to dogs, the concentration in the aqueous humour one hour later is about 33% of that in the blood, rising to a maximum of about 61% four hours after administration (Bellows & Chinn, 1939); when 100 mg. sulphapyridine was applied locally to the conjunctiva (of rats) the concentration one hour later was 47 mg. per 100 cm.³ in the conjunctiva, 30 mg. in the cornea, and only 5 mg. in the aqueous humour (Pan, 1941). The content of sulphapyridine in the pancreatic juice (of cats) after its administration by mouth, is slightly less than that of the blood (Taylor & Ågren, 1940); [for bile, see under "Excretion."] Sulphanilamide is also found in menstrual blood; but in the normal secretion of the cervix uteri it is present in such small amounts that its bacteriostatic action is problematic.

The fetus. Sulphonamides pass through the placenta into the foetal circulation, and there are therefore possibilities of toxic and of therapeutic action. Speert (1943) recommends that in order to prevent bacterial invasion of the foetal blood vessels in cases of prolonged labour with ruptured membranes, and in cases where it is desired to protect the foetus against intrapartum infection by gonococci from the mother, the woman in labour should be given a single intravenous dose of 5 g. sodium sulphadiazine; during the next few hours concentrations of 9-11 mg. per 100 cm.³ will be maintained in the foetal blood and 10-20 mg. in the maternal blood. This procedure involves a possible (but low) risk of renal obstruction in the mother. Although prolonged treatment with sulphanilamide is injurious to the foetus (Adair, Hessel-tine & Hac, 1938; Speert, 1940), in animals or in human beings the danger from a single dose is probably small (Philipp, 1941). In 18 cases treated by Speert (1943) and in 35 cases reported by Kayser (1941) the children appeared completely unharmed; on the other hand, the baby of one of 13 mothers taking sulphanilamide suffered from severe anaemia and jaundice which may have been due to the treatment (Heckel, 1941).

Combination of sulphonamides with plasma proteins. Part of the sulphonamide in the plasma is bound in some way to the plasma proteins, and is not free to pass through a dialysis membrane. The combination to protein cannot be very strong, as sulphonamides are not precipitated to any large extent when the proteins of blood or serum are thrown down

by trichloroacetic acid in the first stage of Marshall's quantitative test. The combination apparently involves principally the plasma albumin, while the globulin and lipoids are not concerned (Davis, 1942). The higher the concentration of sulphonamide, the smaller the percentage of bound drug; the figures below refer to blood-concentrations of the therapeutic range (2–20 mg. per 100 cm.³). The amount bound is approximately proportional to the amount of albumin present. The binding is not diminished by denaturation of the protein with ultra-violet light (Davis, 1943). Similarly, red prontosil is combined with the albumin of the serum but not with the globulin, as was shown by Schönholzer (1940), using a cataphoresis technique. The extent to which this binding occurs differs with the different compounds, as is shown below (Davis, 1942; Heinemann, 1943):

sulphanilamide	. . .	12–20 % bound
sulphapyridine	. . .	40–45 % „
sulphathiazole	. . .	75–80 % „
sulphadiazine	. . .	55–60 % „

Compounds similar to the sulphonamides but lacking the *p*-amino group, and acetyl derivatives of sulphonamides are bound to the proteins in the same way (Davis & Wood, 1942). Apparently the bound drug is not bacteriostatic, although, as the combination is loose, it forms a store of potential activity. The occurrence of this combination with protein probably explains the different distribution of the various compounds between plasma and erythrocytes, and between blood and cerebrospinal fluid, which have been described above. In fact the calculated distribution between blood and a dialysate through a membrane permeable to sulphonamides, but not to protein, agrees closely with that observed clinically between blood and cerebrospinal fluid. Such combinations with proteins may conceivably play a part in the production of such sensitization phenomena as drug-fever and specific skin sensitivity.

Metabolism of Sulphonamides

As is well known, much of the sulphonamide compound introduced into the body is conjugated, especially with acetate, to form acetyl derivatives which are therapeutically inert, although equal in toxicity to the original sulphonamide. Sulphanilamide and sulphapyridine are more readily acetylated than sulphathiazole and sulphadiazine. On the average, about 20 % of sulphanilamide in the blood and about 25–60 % of that in the urine is in the conjugated state. With sulphapyridine, about 33 % (10–45 %) of the total compound in the blood and about half of that in the urine is acetylated in man (Kinsman, Moore & Harrison, 1940). With sulphadiazine, the acetylated form accounts for about 10 % of the compound in the blood and for about 25–33 % of that in the urine (Peterson, Strauss, Taylor & Finland, 1941). With sulphathiazole, about 20 % of the compound in the blood is acetylated (Frisk, 1940a, 1940b), or 0–30 % (average 12 %) (Sadusk, Blake & Seymour, 1940).

The site of acetylation seems to be mostly in the liver (Harris & Klein, 1938), though in some animals other organs also can bring about this conjugation. In rabbits it occurs only in the liver; in cats it occurs in both liver and spleen (Van Winkle & Cutting, 1940). Curiously, acetylation can also be brought about by fowl pox tissue *in vitro* (Goth, 1942). Apparently acetylation *in vitro* is dependent on the intact liver cell, and aerobic respiration is essential. Acetylation of sulphanilamide can be increased in mice by giving sodium acetate with the drug; the acute toxicity of the sulphanilamide is somewhat diminished but its curative action for streptococcal infections is said to be unchanged (James, 1939). It has been denied that the first step in the process of acetylation is the conversion of sulphanilamide into

the *p*-hydroxylamino derivative—HO.HN \langle SO₂.NH₂

(Thorpe, Williams & Shelswell, 1940). When an acetyl-sulphonamide is given by mouth, some of it is deacetylated in the body liberating a small amount of the active sulphonamide; part of this reversal of the conjugation occurs in the liver (cat) (Van Winkle & Cutting, 1940), and the kidney (chicken) also contains an enzyme which will produce this effect (Shaffer, 1942).

Besides the sulphonamide inactivated by acetylation, there is evidence that part is combined with other compounds (especially glucuronic acid), or is degraded by other chemical processes. Thus, if sulphapyridine is fed to rats it increases

the output of glucuronic acid, and it is suggested that 40 % of the so-called “free” sulphapyridine excreted may really be glucuronate (Scudi & Robinson, 1941); sulphanilamide does not stimulate this output of glucuronate, while sulphathiazole does so only moderately. In dogs, part of the sulphapyridine is excreted as a glucuronate attached to a hydroxyl group on the pyridine ring of sulphapyridine (Weber, Lulich & Major, 1943). Glucuronic acid, given to rats, inhibits the conjugation of sulphanilamide (Martin, Rennebaum & Thompson, 1941). When sulphanilamide is given to rabbits there is an increase in the amount of ethereal sulphate excreted in the urine; probably 6–12 % of the sulphanilamide is converted into a phenolic form—

HO \langle SO₂.NH₂—and excreted as a conjugated sulphate

(Shelswell & Williams, 1940). Rimington & Hemmings (1939) showed that part of the sulphonamide may be oxidised. But although these various reports are suggestive, they are either incomplete or lacking in confirmation, and it seems clear that acetylation accounts for the greater part of the sulphonamide which is inactivated in the body. On the other hand, it has been shown by Simesen (1941a) that during the first day (in mice) up to 50 % of the sulphanilamide may be destroyed in some way at present unknown, while 40–50 % of sulphathiazole and of sulphacetamide is destroyed in this time; 40–50 % of sulphapyridine is destroyed in 2–3 days, and 70 % of uliron in 3–4 days. Alexander (1943) has confirmed this by giving sulphanilamide to mice and analysing the amount found in the excreta and in the (minced) body after various periods.

Excretion

i. *Urine*. The main excretion of sulphonamides is through the kidney, the amounts passing out by other routes being comparatively insignificant. Part is excreted unchanged and part as the acetyl derivative, as has been described above. Apparently sulphanilamide passes out from the plasma into the glomerular filtrate and some of it is reabsorbed in the tubules. In dogs, the sulphanilamide clearance is 20–30 % of the creatinine clearance (only slight reabsorption in the tubules), so presumably 60–70 % of the sulphanilamide in the glomerular filtrate is reabsorbed. The clearance is independent of the plasma level, but increases as the flow of urine is increased. In rabbits, the clearance of sulphanilamide is 30–40 % that of creatinine and inulin, but the clearance of acetyl sulphanilamide is the same as that of these two compounds; presumably acetyl-sulphanilamide is not reabsorbed in the tubules (Loomis, Hubbard & Koepf, 1943). The average renal clearances in man for the original sulphonamides and their acetyl derivatives respectively are:

sulphapyridine	. 23 and 58 cm. ³ of plasma per minute
sulphathiazole	. 43 „ 55 „ „ „ „ „
sulphadiazine	. 31 „ 59 „ „ „ „ „ „

i.e. the amount of compound present in this volume of plasma is excreted by the kidney per minute.

As regards the proportion of the dose excreted in the urine various estimations have been given:

Sulphapyridine (usual clinical dosage): 60–90 % (Frisk, 1940a); or about 30 % (22–56 %) (Kinsman, Moore & Harrison, 1940) appears in the urine, about half being in the conjugated form.

Sulphathiazole: Daily excretion amounts to 75 % of the intake (Simesen, 1941b), to 86–92 % of the intake (Frisk, 1940b) or to 100 % (Spink & Hansen, 1940).

Sulphadiazine: When 4–5 g. is given orally, 60 % is excreted in urine in 24 hours, and 75 % in 72 hours; a quarter to a third is in the conjugated form (Peterson, Strauss *et al.*, 1941). Other data are given by Ratish, Shackman & Bullowa (1942); Reinhold, Flippin *et al.* (1941); and Sadusk, Blake & Seymour (1940). When it is desired to increase the excretion of sulphadiazine (*e.g.* because of agranulocytosis) sodium bicarbonate should be given; to decrease the concentration in the urine (*e.g.* because of renal complications) large volumes of 5–10 % glucose should be injected intravenously or much water may be given by mouth; intravenous injection of saline is less effective (Peterson, Goodwin & Finland, 1943).

ii. *Fæces*. The work of Marshall, Bratton *et al.* (1940) on sulphaguanidine and the treatment of bacillary dysentery has directed attention to the amount of sulphonamide

appearing in the faeces. Practically all such compound represents the portion which has not been absorbed during passage down the alimentary canal; very little represents true excretion by the bile or by the mucous membrane of the large intestine. Thus, when sulphaguanidine is injected subcutaneously into cats, only very small amounts appear in the faeces (Hawking, 1942b). When given as a short therapeutic course to man, sulphapyridine, sulphathiazole, sulphadiazine and sulphanilbenzamide reach the faeces only in small concentrations, e.g. 0-70 mg. per 100 cm.³ (Hawking, 1942a). Ulliron apparently reaches the faeces in about the same amount as sulphaguanidine; when 12-18 g. is given during 6 days, about 7 g. appears in the faeces and about 3-4 g. in the urine (Reimers, 1939; Marquardt, 1938). But no report on the use of ulliron for bacillary dysentery has appeared.

iii. *Bile.* Sulphanilamide and other sulphonamides appear in the bile only in concentrations about the same as those in the blood; no large amount of the acetyl derivative appears, so that, although it is formed in the liver, it is not excreted by this route (Hubbard & Anderson, 1940; Spink, Bergh & Jermsta, 1941; Hubbard & Butsch, 1941). Accordingly sulphonamides are unlikely to have any special influence in cholecystitis, beyond their general influence on inflammation anywhere in the body.

iv. *Other secretions.* Sulphonamides appear in most of the other excretions and secretions in concentrations similar to those of the blood. Sulphapyridine injected parenterally appears in the gastric juice (apparently by a process of physical diffusion, Davenport, 1942), and this may be the explanation of the vomiting which may occur in such patients. Sulphathiazole appears in the tears in concentrations of 0.1-1.0 mg. per 100 cm.³, but this is not the direct cause of the conjunctivitis which sometimes develops; such conjunctivitis is probably due to acquired sensitivity (Turkell & Wilhelm, 1941).

v. *Milk.* Sulphonamides appear in the milk of lactating women in amounts similar to those of the plasma. Thus during a therapeutic course, the milk may contain sulphanilamide up to 9 mg. per 100 cm.³ (Hepburn, Paxson & Rogers, 1942), sulphapyridine 3-13 mg. per 100 cm.³ (Föllmer, 1941), or sulphathiazole 0.5-1.5 mg. per 100 cm.³ (Rieben & Drucey, 1942), and the infant may receive sulphapyridine 30-40 mg. per day or sulphathiazole about 4 mg. per day. Other studies have been made by Cibils Aguirre, Calcarami, Aguilar Giraldes & Berisso (1942). It is the general opinion that the amount appearing in the milk of the mother is too small to exert any effect, toxic or therapeutic, upon the infant.

Blood Concentrations

The table shows typical blood-concentrations following the administration of the different sulphonamides:

Compound	Dose	Blood Concentration mg. per 100 cm. ³		Reference
		Free	Total	
Sulphanilamide	4 g.	4*		
Sulphapyridine	2-4 g. 2-4g. followed by 1 g. 4- hourly	2 (0.5-5.0)* 4.2-6.5	2.6 5.6-8.6	Kinsman, Moore & Harrison (1940)
Sulphathiazole	1 g. 4-hourly 2 " " 3 " "	4.6 (1.6-8.7) 6 (2.2-13.2) 6.5 (3.0-9.6)		Melton (1941)
Sulphadiazine	2 g. 5 g. 4-5 g. 3 g. followed by 1 g. 4- hourly	2.0-3.3* 3.6-5.5* 8.5 (6.7-10.8) (after 24 hours 2-4) 9.5 (4.4-19.0)	9.9 (7.9- 12.6) 11.3	Ratish, Shack- man & Bul- lowa (1942) Peterson, Strauss <i>et al.</i> (1941) Reinhold, Flippin <i>et al.</i> (1941)
Sulphamezathine	4 g. followed by 2 g. 6- hourly	6 (2-13)		Macartney <i>et al.</i> (1942)
Sulphamerazine	3 g. followed by 1 g. 6-8- hourly	10.3 (3.5- 15.0)		Murphy, Clark & Flippin (1943)
Sulphaguanidine	1-7 g.	1.5-4.0*		Marshall, Brat- ton <i>et al.</i> (1940)
Succinyl sulphathiazole	17 g. followed by 3 g. 4- hourly	0.5-1.0 (sul- phathiazole)	1.0-2.0 (succinyl sulpha- thiazole)	Poth & Knott (1942)

* Blood concentration at about 4 hours after single dose is taken.

Solubilities of Sulphonamide Compounds

The solubilities of the various sulphonamide compounds and their acetyl derivatives are often important. The table shows the solubilities of the sulphonamides and their acetyl derivatives in mg. per 100 cm.³.

Compound	Water 16- 17° C.	Water 37° C.	Serum 37° C.	Urine 37° C.	
				Acid	Alkaline
Sulphanilamide .	440	1500	1970		-1500
Sulphapyridine .	17	52	61	39 (pH 5.4)	89 (pH 8.2)
Sulphathiazole .	36	96	184- 330	102 (pH 5.4)	359 (pH 8.2)
Sulphadiazine .	7.8	15	160	18 (pH 5.5)	52 (pH 7.5)
Sulphaguanidine .		220			220 (pH 7.1)
Sulphacetamide .	460	1100			2200
Succinyl sulphathiazole		70		191 (pH 5.5)	297 (pH 7.5)
Sulphamezathine .		190			110 (pH 7.0)
Sulphamerazine .					
Acetyl sulphanilamide.		534			
sulphapyridine .		24	33	11 (pH 5.4)	89 (pH 8.2)
sulphathiazole .		6	104	10 (pH 5.4)	265 (pH 8.2)
sulphadiazine .		30	126- 198	26 (pH 5.5)	248 (pH 7.5)
sulphaguanidine		40			81 (pH 7.1)
sulphameza- thine		115		115 (pH 5.5)	176 (pH 7.5)
sulphamerazine					330 (pH 7.0)

The solubility of the compounds named above is greatly increased by making it in the excret sulphonamides of The sodi up to about 1 part in 3.

Action on Various Organs

Examined by the methods of classical pharmacology, sulphonamides are comparatively inert and sulphanilamide has no effect upon intestine, uterus, heart or blood pressure. Given in toxic doses to laboratory animals, it depresses the cerebral cortex and excites subcortical centres, producing coma followed by a condition resembling decerebrate rigidity (Hawking, 1937; Marshall, Cutting & Emerson, 1938). A case has been recorded (Cutts & Bowman, 1941) of a man who was given by mistake 30 g. sodium sulphapyridine during a 10-hour period. The main nervous symptoms were restlessness, vomiting and hiccough, but no convulsions, twitching or loss of mental lucidity. When monkeys are given repeated sublethal doses of sulphapyridine or sulphathiazole, a characteristic symptom-complex is produced, consisting of anorexia, increasing nausea, with or without vomiting, and diarrhoea. The commoner toxic effects which occur in man are too well known to require detailed description. They may be classified as: Irritation of alimentary canal (nausea and vomiting); effects on blood cells and bone marrow (haemolytic anaemia, agranulocytosis, thrombocytopenia); effects on blood pigments (cyanosis, methaemoglobinemia, sulphamoglobinemia); sensitization phenomena (drug-fever, skin rashes); degeneration of particular organs (jaundice and liver damage, peripheral neuritis); and effects on the brain (mental depression, headache and dizziness).

Effect on Acid-Base Balance

Sulphanilamide tends to cause a shift in the reaction of the body fluids towards the acid side, bicarbonate being lost from the blood. It has been shown that this effect is primarily due to the renal excretion of more bicarbonate (*i.e.* the kidney cells reabsorb less bicarbonate from the glomerular filtrate as it flows down the tubules) (McChesney, Sprague & Marshall, 1941; Höber, 1942); while the hyperpnoea and loss of carbon dioxide from the lungs is a secondary compensation. Accordingly, this effect can be corrected for clinical purposes by giving sodium bicarbonate in doses equal to those of sulphanilamide. There is some evidence that this action of sulphanilamide may possibly be connected with the ability of sulphanilamide to inhibit carbonic anhydrase, the enzyme which catalyses the liberation of carbon dioxide from the carbonate of the plasma; as was shown by Mann & Keilin (1940), this enzyme is strongly and reversibly inhibited by sulphanilamide, but not by sulphonamides in which substitutions have been inserted on the $-SO_2NH_2$ group, e.g. sulphathiazole. A blood concentration of 3-4 mg. sulphanilamide per 100 cm.³ does not affect the excretion of

carbon dioxide from the lungs in men at rest, but in exhausting exercise there is some hindrance; and men taking 2-3 g. sulphanilamide daily are handicapped mentally and physically when required to perform exacting or strenuous work (Roughton, Dill, Darling, Graybiel, Knehr & Talbott, 1941). On the other hand, men taking 2-4 g. sulphathiazole or sulphadiazine are not handicapped in this way (Roughton, Darling, Forbes, Horvath, Robinson & Talbott, 1942).

Other Actions

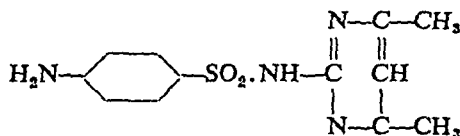
Sulphapyridine has some antipyretic action, which may partly account for the rapid fall of temperature which it causes in patients with pneumonia (Nicolai, 1941). The action of sulphonamides on isolated tissue cells, and their behaviour when applied locally to wounds has been described by Hawking (1943).

Relation to Diet

In laboratory animals which have been placed on a high-protein diet, compared with those on a low-protein diet, the toxicity of sulphonamides is diminished, but so also is their therapeutic action against streptococcal infections; apparently the high-protein diet produces increased excretion of the sulphonamides, and the blood concentration is therefore lower than usual. These facts are important for the standardization of laboratory tests, but not for clinical purposes (Smith, Lillie & Stohlman, 1941; Rosenthal, 1941). When rats are placed on purified diets containing sulphaguanidine or succinyl sulphathiazole (which suppress the growth of coliform bacilli of the large intestine) growth is diminished and various pathological lesions are caused, e.g. aplasia of the bone marrow, hyaline sclerosis of blood vessels and viscera, dermatitis, and hypertrophy of the thyroid gland. It is considered that these effects are probably due to lack of substances such as folic acid, which are synthesized by the bacteria of the large bowel (Ashburn, Daft, Endicott & Sebrell, 1942; Black, Overman, Elvehjem & Link, 1942; Mackenzie, Mackenzie & McCollum, 1941).

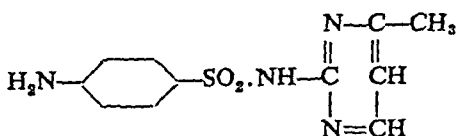
Notes on the Pharmacology of Some Newer Sulphonamides

Sulphamezathine: [2-(p-aminobenzene-sulphonamido)-4:6-dimethyl-pyrimidine].



Synthesized by Sprague, Kissinger & Lincoln, 1941, and by others, and introduced (as sulphamethazine) for clinical use by Macartney *et al.* 1942. More soluble than sulphadiazine or sulphamerazine. Rapidly absorbed from the intestine, but slowly excreted, so that a high blood-concentration can be produced by moderate dosage. When 4 g. is given by mouth for pneumonia, followed by 2 g. every 6 hours (or 1 g. every 4 hours), the blood-concentration of free sulphonamide reaches 8 mg. per 100 cm.³ in 1-3 hours and the subsequent blood level ranges from 2-13 (average 6 mg.) per 100 cm.³. The total recovery in the urine is usually about 50% of the amount ingested. Judged according to equal blood-concentrations, the toxicity and therapeutic potency are similar to those of sulphadiazine. Although both sulphamezathine and its acetyl derivative are comparatively soluble, one case of haematuria and one of urinary suppression occurred in a series of 77 patients (Peters & Easby, 1943).

Sulphamerazine: [2-(p-aminobenzene-sulphonamido)-4-methyl-pyrimidine].

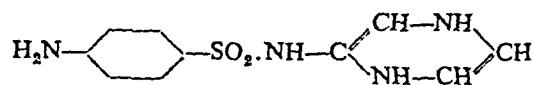


Synthesized by Roblin, Williams, Winnek & English (1940). At first it was not tried clinically for fear that, as a methyl derivative, it might cause peripheral neuritis (cf. uliron and sulphamethylthiazole); but this fear has been shown to be unfounded and it has been the subject of many American papers both pharmacological (Goodwin, Peterson & Finland, 1942; Welch, Mattis,

Latven, Benson & Shiels, 1943; Murphy, Clark & Flippin, 1943) and clinical (Clark, Flippin & Murphy, 1943; Geffer, Rose, Domm & Flippin, 1943; Hall & Spink, 1943; Hageman, Harford, Sobin & Ahrens, 1943).

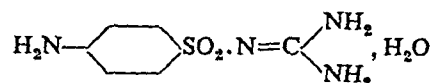
Sulphamerazine is more quickly absorbed than sulphadiazine and more slowly excreted than sulphamezathine, and its blood-concentration therefore rises more quickly and is longer sustained than those of these two other compounds. A dosage of 3 g. (initial) by mouth and 1 g. every 6-8 hours produces a blood-concentration of 8-10 mg. per 100 cm.³. In the blood, 9-15% of the drug is in the acetylated form, and in the urine 37-50%. Urinary excretion accounts for 40% (average) of the ingested drug within 24 hours and 58% within 48 hours. With equal blood-concentrations, the toxicity and therapeutic activity are closely similar to those of sulphadiazine, but an adequate blood-concentration can be maintained by lower and less frequent dosage than in the case of sulphadiazine. An average blood-concentration of 27 mg. (but not of 32 mg.) per 100 cm.³ can be tolerated by monkeys for long periods. Although the solubility of sulphamerazine and acetyl sulphamerazine is relatively high, giving rise to the expectation that renal complications would be infrequent, 6 cases of definite renal symptoms occurred in about 400 cases.

Sulphapyrazine: [2-(p-aminobenzene-sulphonamido)-pyrazine].



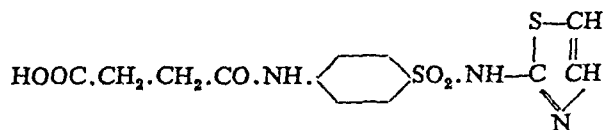
Small doses of this compound lead to a relatively high blood-concentration while large doses cause no corresponding increase. Consequently, at a low dose level, sulphapyrazine is more active than other sulphonamides, but at a high dose level this advantage disappears. Absorption is somewhat irregular, making its therapeutic effect uncertain; this irregularity would be a handicap for clinical use. As absorption in the intestine is incomplete, large proportions of the ingested dose reach the faeces, and this compound would therefore appear to be suitable for the treatment of bacillary dysentery; but no clinical reports have yet appeared about its use for this condition (Rueggsegger, Hamburger, Turk, Spies & Blankenhorn, 1941; Schmidt & Sesler, 1943; White, 1942).

Sulphaguanidine: [p-aminobenzene-sulphonyl-guanidine].



Sulphaguanidine is poorly absorbed when given by mouth, and a considerable portion appears in the faeces, this being the reason which led to its use in the treatment of bacillary dysentery. After doses of 1-7 g. per 70 kg. man, the blood-concentration (free) is about 1.5-4 mg. per 100 cm.³, the peak occurring after about 4 hours; about 25-30% of the compound in the blood is acetylated. The proportion excreted in the urine after a single dose of 1-7 g. is 10-60%, of which two-thirds are free and one-third is acetylated (Marshall, Bratton *et al.*, 1940). After a course of 9 g. during 24 hours to a patient, 1.3 g. was recovered from the faeces, and 3.1 g. from the urine in 48 hours (Hawking, 1942a). Penetration into the cerebrospinal fluid is low. In dehydrated patients with dysentery in the British army in Egypt, sulphaguanidine has occasionally caused blockage of the urinary passages. (See also Hawking, 1942b.)

Succinyl sulphathiazole (sulphasuxidine): [2-(p-succinyl-amino-benzene-sulphonamido)-thiazole].



This compound, which was introduced by Poth & Knotts (1941), is broken down in the intestine, liberating small amounts of sulphathiazole; the growth of the coliform bacilli (but not that of the streptococci) in the large intestine is thereby suppressed and the faeces become semi-fluid and odourless; about 2-4 motions are passed per day. The compound is recommended for dysentery and for the preparation of patients before undergoing operations on the large intestine. The standard dosage in man is 0.25 g. per kg. initially, and 0.04 g. per kg. 6 times daily for maintenance. The urine contains about 5% of the total dose administered. The blood contains about 0.5-1.0 mg. free sulphathiazole per 100 cm.³ and 1.0-2.0 mg. total (i.e. acetyl sulphathiazole plus succinyl sulphathiazole) (Poth & Knotts, 1942; Poth, 1942).

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295

NOTE ON THE BIOLOGICAL STANDARDISATION OF NEOARSPHENAMINE

FRANK HAWKING, D.M.

National Institute for Medical Research, London

Arsphenamine, or salvarsan, the first important chemotherapeutic preparation to be discovered, was introduced by Ehrlich in the early years of the century. After the war of 1914–18, an improved modification of it, neoarsphenamine, became the main remedy for syphilis. As both these compounds were non-crystalline substances, they could not be purified and identified by the ordinary methods, and chemical tests failed to detect the obscure differences which might lead to wide and dangerous variations in toxicity between different batches of the same product. Accordingly, biological tests were necessary to ensure (i) that a given batch was not abnormally toxic, and (ii) that it was not deficient in the proper therapeutic activity, as evidenced by its action on laboratory infections of *Trypanosoma equiperdum* in mice.

At first the biological tests were arbitrarily chosen on an empirical basis, and they differed greatly from one country to another. This position was radically altered by the meeting of the International Conference on Biological Standards at Geneva in 1925. The Conference recommended that *standard* preparations of each of the main compounds of the arseno-benzene group should be produced, and (ii) that each batch of the remedy manufactured by the industrial firms should be tested, so as to show that its toxicity and its therapeutic potency did not diverge too far from that of the standard preparation. At a later Conference it was agreed that manufactured batches issued for clinical use should not diverge from the standard by more than 20 %. The practical implications of these recommendations were worked out in 1929 by Durham, Gaddum, & Marchal of the Department of Biological Standards of the *Medical Research Council*; they determined the dose-response curve for neoarsphenamine, using large numbers of mice, and subjected the data to statistical analysis. Later the statistical aspects were developed in greater detail by Gaddum (1933). The International Standard Preparation of neoarsphenamine was prepared in the first place by Professor Kolle of the *Georg Speyer Haus*, Frankfurt, and samples of it were issued to the Department of Biological Standards in each of the main manufacturing countries. In each country a subsidiary standard was prepared, identical in toxicity and therapeutic potency with the International Standard Preparation, and this subsidiary standard was used for routine purposes. At the outbreak of the present war in 1939, the available supplies of the original International Standard Preparation were limited, so a new standard preparation was obtained in Great Britain; it was examined by biological assay in the Department of Biological Standards of the *Medical Research Council*, and in other British laboratories, and was shown to be identical in toxicity and therapeutic potency with the previous International Standard Preparation. Ampoules of this product were stored in several different parts of the country, so as to escape complete annihilation during air-raids; and this preparation is now available for standardisation in Great Britain and other countries as it is required.

Biological Testing in Britain

The various International Conferences on Biological Standards left the exact details of the biological tests to be regulated by the appropriate authority of each country according to its discretion. The tests for undue toxicity adopted in Great Britain from 1932 onwards have been as follows:

i. *Tests on mice.* A dose of 0.3 cm.³ of a 2 % solution of the sample of neoarsphenamine is injected intravenously into 10 mice, weighing 13–15 g. If not more than 2 mice

die within 3 days, the batch is passed without further test. If more than 2 mice die, 20 more mice are treated; and if not more than 15 mice out of the total of 30 mice die, the batch is passed. Under the conditions of the assay (which are minutely prescribed) it was initially calculated that this test ought to be passed by almost all batches having a toxicity not greater than 120 % of that of the International Standard Preparation.

ii. *Tests on rats.* A dose of 0.225 mg. per g. body weight in 5 % solution is given intravenously to each of 5 rats weighing about 100 g. It is expected that none of these animals shall die within 7 days. This test was introduced to detect certain irregularities (e.g. the formation of toxic large colloidal aggregates in solution) which escaped detection by the mouse test, to which it is really secondary.

Control of Manufacture and Marketing

British firms may manufacture neoarsphenamine for commercial issue only after they have received a licence from the Ministry of Health; such licences are granted only after the firm has shown that it is capable of preparing a product of the required high standard, and after its premises have been inspected and found satisfactory. At the present moment, four British firms hold these licences. The official tests are carried out by the pharmacologists of the firm for each batch of the product, and the experimental protocols are submitted for inspection to the Department of Biological Standards of the *Medical Research Council*. In certain cases the Department may carry out additional tests of its own. When the Department is satisfied that the batch has passed the official tests, it issues a licence allowing the commercial sale of the batch in question.

Results of Further Experience

When the regulations for these tests were laid down it was assumed that the sensitivity of mice, maintained under uniform conditions, was a constant quantity, i.e. that a given dose administered to a large group of mice would always cause the same mortality. Further experience has shown that this assumption is not altogether correct, and that the sensitivity of mice can be modified by any change in their environment or past history. Many aspects of the matter were investigated by Miss W. I. Strangeways, of the Department of Biological Standards. The sensitivity of a group of mice depends upon the breed of the mice, upon their age, weight, diet and other circumstances. It is also affected by the interval between the last feeding time and the administration of the drug, by the temperature of the room and by the concentration of the solution of neoarsphenamine used. Attempts have been made to exclude as many as possible of these sources of error by minutely prescribing the conditions of maintenance of the mice before, during, and after the test; but it is clear that these measures are not altogether satisfactory. The only way in which the test can be carried out accurately, is to make a direct comparison between the tested batch and a standard preparation at each time of testing. Since the influence of the environmental factors is the same for both compounds, the errors due to them are excluded by this means. A direct comparison of this kind is already made by some of the firms which manufacture neoarsphenamine and, after the war, the official tests will be modified so that this will be the case.

The test for therapeutic potency, which was in force from 1932 onwards, depended on administering the product under test and the standard preparation in dosages of 0.03 mg.

and 0.025 mg. per g. to groups of 5 mice, one group for each dosage of each preparation, i.e. 4 groups in all. The mice carried a suitable infection of *Trypanosoma equiperdum*. The blood of the mice was examined on the seven succeeding days, and it was required that the product under test should show a curative action "not significantly less potent" than that of the standard. In borderline cases, the interpretation of the phrase "not significantly less potent" was often difficult, the test was not suitable for statistical analysis, and some of the details of counting the trypanosomes in the blood of the infected mice were unduly laborious.

Reorganisation of the Tests

In view of the considerations discussed above, the tests were reorganised in 1942. Details of the new arrangement

of the tests have recently been published by the writer (Hawking, 1943). By means of these tests, the safety (freedom from abnormal toxicity) and therapeutic efficiency of all batches of nearsphenamine manufactured and issued for use in Great Britain is assured.

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REVIEW OF SELECTED PAPERS

Modes of Drug Action

The papers which are reviewed in this section were read at a discussion held by the Faraday Society on "Modes of Drug Action." The discussion, with Professor E. K. Rideal in the Chair, opened with a General Introductory Address (1943, *Trans. Faraday Soc.* 39, 319) by Sir Henry Dale, President of the Royal Society and former Director of the National Institute for Medical Research. Sir Henry welcomed the growing interest shown by physical chemists in medical research problems. It was a truism to say that future explanations of life processes would be expressed in terms of complicated and labile physico-chemical systems. There had been a tendency to over-simplification in interpretations of the effects of chemical substances on physiological functions.

Paul Ehrlich was the great pioneer of that aspect of the subject which dealt with the chemotherapy of infections. His conceptions and terminology still had value as a framework for working hypotheses, but should not be confused with reality. Referring to the study of progressive changes in the actions of series of related compounds, Sir Henry said that anomalies might prove of more fundamental interest than regularities.

He then paid a tribute to the value of the work of the late Professor Warrington Yorke, and referred particularly to his investigations on arsenic-resistance in trypanosomes. He concluded by pointing out that the papers to be read provided evidence of a definite advance in knowledge of the subjects under discussion. For example, in place of labels for hypothetical mechanisms, there was a more realistic conception of interference with vital enzyme systems. The present convergent attack by so many different kinds of experts held promise of important gains to knowledge.

296

BIOLOGICAL ASPECTS: the Antagonism of Drugs

by J. H. Gaddum, *Transactions of the Faraday Society*, 39, 323-333, December 1943

Many recent advances in our knowledge of how drugs act are based on quantitative studies of the extent to which one drug can suppress or "antagonise" the action of another drug. Such an antidote may counteract the effect of a poison (or other drug) in different ways. The two most important ways are by neutralisation (i.e. changing the poison into an inert compound by combining with it or by some other means) or by competition (i.e. competing with the poison for combination with certain hypothetical chemical groups which are in some way essential to the life of the tissue).

i. *Antagonism by neutralisation.* A good example of this is the neutralisation by compounds containing —SH groups of the effects of mercuric chloride or organic arsenical compounds. Chick (1908) has shown that the lethal action of mercuric chloride upon bacteria can be reversed (if this has not gone too far) by the addition of hydrogen disulphide (H—SH). Voegtlin (1925) showed that the lethal action of compounds of the type R—As=O upon trypanosomes or upon rats could be prevented by the presence of —SH

compounds. Fildes & Richardson (1937) have shown that *Staphylococcus* and other organisms require —SH compounds for growth. It has been suggested that mercuric chloride and organic arsenical compounds combine with —SH groups in the organisms. In this way the —SH group is "blocked" or rendered inert, and the organism can no longer continue the processes necessary for life. On the other hand all the observed facts can equally well be explained by the view that the —SH compounds act by combining with the poison (mercuric chloride or arsenical) outside the cell, and thus diminishing the quantity of poison left to act on the organism. A considerable excess of the —SH compound is required to prevent action, e.g. about twice as much glutathione as arsenical compound. As neutralising antidotes can act only by reducing the concentration of free poison (which can be done also by mere dilution) their study is unlikely to lead to new pharmacological knowledge.

ii. *Antagonism by competition.* Many drugs are believed to combine with certain hypothetical receptors in the cell, as a necessary first stage of their action. After this combination has been formed, the drug may produce some specific pharmacological effect or it may merely "block up" the receptor and prevent its use by some more active drug. This process of competition and of blocking has long been known to students of enzymes. Often substances chemically allied to the normal substrate of the enzymes will combine with it and block it in this way. The best known example discovered by Woods (1940) is the way in which sulphanilamide competes with *p*-aminobenzoic acid for combination with some receptor which is essential for the normal multiplication of the bacterium. Another example, which has been studied in great detail, is the competition between oxygen and carbon monoxide for combination with hæmoglobin; in this instance carboxyhæmoglobin is 240 times as stable as oxyhæmoglobin and accordingly carbon monoxide is 240 times more active than oxygen in this reaction.

The author gives mathematical equations to express the quantitative relations between each of these kinds of poison and antidote. But the two types of curve are fairly similar, and it would probably not be possible to distinguish between the two types of antagonism by a study of the quantitative relationships. The distinction can be made only from independent evidence that the drugs combine with one another, or that they are likely to compete.

Other types of antagonism between drugs are also known. For example, indole-acrylate inhibits the growth of certain bacteria, apparently by interfering with the formation of tryptophane from indole; a small amount of tryptophane completely antagonises this inhibition of growth because the source of obstruction (of production of tryptophane) is thus circumvented.

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THE CELL METABOLISM OF THE MALARIA PARASITE IN RELATION TO THE MODE OF ACTION OF ANTIMALARIAL DRUGS

by S. R. Christophers, *Transactions of the Faraday Society*, 39, 333-339, December 1943

The author, Sir Richard Christophers, F.R.S., is well known for his important work in India on malaria. Since his return to England he has worked on this subject in London and at Cambridge.

Investigations on the metabolism of malaria parasites were commenced by Christophers & Fulton (1938) and their results have since been confirmed and extended by various American workers. Most of the work has been done with *Plasmodium knowlesi*, a parasite which is virulent for certain monkeys, but bird plasmodia have also been used. The whole blood from a heavily infected monkey or bird may be used, or the parasites can be separated from the blood corpuscles and obtained without great damage in a free state. The parasites or parasitised blood are placed in a Barcroft differential manometer, and the oxygen consumption is measured in the usual way. By these means it has been established that:

- i. Suspensions of parasites consume oxygen at a high rate, much higher (e.g. $\times 300$) than does normal blood.
- ii. The uptake of oxygen is proportional to the amount of parasites present and to their stage of development.
- iii. The uptake is much greater ($\times 10$) with the large forms of the parasite than with the small ones.
- iv. The uptake can be inhibited by even minute traces of certain drugs.

The oxygen uptake is about 2.17 ml. per 10^{10} parasites per hour; this is about $\frac{1}{8}$ of the oxygen consumption of trypanosomes, which, however, are much larger. Glucose is utilised, but the oxygen consumption of malaria parasites does not depend so closely upon the supply of glucose, as does that of trypanosomes. The malaria parasites use glucose at the rate of 18 mg. per 10^{10} parasites per hour, and one molecule of oxygen is used for each molecule of glucose consumed. Half of the glucose which is destroyed is converted into lactic acid, and the other half is incompletely oxidised. In addition to glucose, laevulose, maltose, mannose, glycerol and lactate can be used by the parasites, but not other sugars. The respiratory quotient is about 0.78-0.86, which shows that much of the energy is derived from the oxidation of carbohydrate. This is in contrast to the respiratory quotient of trypanosomes, which is only 0.2, indicating that much of their metabolism is anaerobic. Acid is liberated by plasmodia to a varying extent. The oxidation process can be inhibited by cyanide, and it is probable that an enzyme-system containing hydrogenase and cytochrome is concerned.

The action of drugs which kill the parasites probably depends upon their interference with enzyme-systems; at any rate this forms a good working hypothesis. Antimalarial drugs such as quinine, atabrin and plasmoquin actively inhibit the oxygen consumption of *P. knowlesi*, just as they exert a therapeutic action upon malaria *in vivo*. Sulphanilamide, sodium sulphathiazole and sodium sulphapyridine are as active in inhibiting the oxygen consumption *in vitro* as they are active in curing the infection *in vivo* (Coggeshall & Maier, 1941).

These investigations are not likely to lead to the discovery of a new antimalarial drug by some short and easy way; but they are especially important because they may show what particular link in the cell respiratory mechanism is broken by a certain type of inhibiting drug, e.g. quinine, atabrin, etc. If this were discovered, the biological chemotherapist would be in a much better position to collaborate with the organic chemist in his synthesis of new anti-malarial compounds. All drugs probably do not act in the same way, but quinine, mepacrine (atabrin) and plasmoquin probably all act as described. The most outstanding feature of all these three compounds is that they are complex organic bases. Diminution of their basic groups diminishes their therapeutic activity. The dissociation constants (pK) and the solubility of the compounds determine most of the reactions of any given base in a test tube. The author considers that possibly the inhibitory and antimalarial effects of these compounds are an indirect effect of their basic character rather than a direct result of their molecular structure.

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298

THE BLOOD-BRAIN BARRIER AND CEREBRO-SPINAL FLUID IN RELATION TO THE EFFICACY OF SLEEPING-SICKNESS DRUGS

by E. M. Lourie, *Transactions of the Faraday Society*, 39, 340-348, December 1943

The author of this paper is Head of the Department of Chemotherapy at Liverpool School of Tropical Medicine.

Sleeping sickness, or human trypanosomiasis, is due to infection with *Trypanosoma gambiense*. The infection develops in two stages. In the first stage the trypanosome occurs in the blood, lymphatic organs, and body tissues in general, and it is freely exposed to the action of any drug circulating in the blood. In the second stage the trypanosome multiplies in the brain, and can be reached only by drugs which can pass the barrier which exists between the blood and the central nervous system. In a large proportion of persons suffering from sleeping sickness, the brain is involved when the diagnosis is first made, and consequently the provision of effective drugs which can penetrate into the nervous system is very important.

The term "blood-brain barrier" is functional rather than anatomical, and it is used to indicate the mechanism which exercises a selective control over the passage of substances from blood to brain. The barrier is probably localised for the most part in the walls of the cerebral capillaries, and substances which reach the brain cells from the blood pass through the capillary endothelium into the perivascular and pericellular spaces around the cells. The extent to which actively trypanocidal drugs can pass this barrier is very varied, and cannot be deduced from the results of the customary experiments on mice infected with trypanosomes. Thus, suramin (Bayer 205) is extremely active in destroying trypanosomes in the blood of mice, and it is very effective in the first stage of human trypanosomiasis; but it cannot pass the blood-brain barrier to any appreciable extent, and it is powerless to cure when once the brain has been infected. Conversely, tryparsamide is only moderately active when tested in mice, but it passes the blood-brain barrier readily, and thus is the most effective known remedy in the later stages of the human disease. Up to the present time the search for drugs against sleeping sickness has been conducted mainly by testing their power to cure mice infected with trypanosomes, but as these examples show, there is need for a more direct means of deciding whether a drug can exert a trypanocidal effect beyond the blood-brain barrier. There are technical difficulties in devising such a test. Theoretically it would be desirable to take samples of the perivascular and pericellular fluids of the brain, in order to measure their power to kill trypanosomes. But in actual practice it is impossible to obtain such fluid in appreciable amounts. Cerebrospinal fluid is derived mainly from the choroid plexuses of the cerebral ventricles, and although its composition is often assumed to approximate to that of the pericellular fluid, this is only an assumption which cannot be proved. However, cerebrospinal fluid is the only fluid of the brain which is available for testing in adequate amounts, and it has therefore usually been used for this purpose. Its use is also justified by the fact that when trypanosomes invade the brain, they are located at first in the choroid plexuses and cerebrospinal fluid, while the tissue of the brain is not involved until later.

The first tests on the trypanocidal power of cerebrospinal fluid were made by Voegtlin, Smith, Dyer & Thompson (1923) who used a rather crude method. They trephined the skulls of rabbits and inserted trypanosomes into the subarachnoid space. The test compounds were injected intravenously. After a suitable interval the rabbits were killed and a search was made for the trypanosomes which had been inserted. A more refined method was introduced by Hawking, Hennelly & Quastel (1937), who injected arsenical compounds intravenously into patients suffering from syphilis of the nervous system. After a suitable interval, cerebrospinal fluid was withdrawn and its trypanocidal power was measured *in vitro* by a technique devised by Yorke, Adams & Murga-

troyd (1929). Trypanocidal power of the cerebrospinal fluid due to arsenicals could easily be distinguished from that due to other non-specific causes, by comparing its action on arsenic-resistant trypanosomes with that on normal trypanosomes. By this means it was shown that tryparsamide produced a greater trypanocidal power in the cerebrospinal fluid than any of the other compounds tested. After therapeutic doses of tryparsamide, e.g. 2 g. per adult, the trypanocidal power of the cerebrospinal fluid was maximal in 40 hours and it disappeared in about 70-90 hours. The trypanocidal power was not proportional to the concentration of arsenic in the fluid (as determined chemically), and only a fraction (5-30 %) of the arsenic occurring in the fluid was present as the active trivalent form.

Neoarsphenamide (when given to patients in therapeutic doses) did not appear to penetrate into the cerebrospinal fluid to an appreciable extent; sulpharsphenamide penetrated to a greater extent, but less than did tryparsamide. In later work, Hawking (1940) carried out similar tests on Africans suffering from sleeping sickness, and showed that infection of the nervous system (presumably involving the choroid plexuses and meninges) did not greatly increase or decrease the penetration of tryparsamide into the cerebrospinal fluid, as compared with the fluid of normal persons.

The method of Hawking yielded results which were of direct significance for human therapy, but it suffered from the usual limitations of observations on human subjects, viz. the small number of subjects available and the need to avoid all danger of toxic effects. Accordingly the present author and Dr. H. O. J. Collier have adapted the technique for use with rabbits. Their results are not yet published in detail. They find that although tryparsamide readily renders the cerebrospinal fluid of rabbits trypanocidal, its trivalent derivative (reduced tryparsamide thioglycollate) does not. In their experiments, neoarsphenamide penetrated into the fluid to a considerable extent. Presumably they injected much larger doses into their rabbits than would be safe to employ in man.

The factors which determine the ability of compounds to penetrate the blood-brain barrier are not well understood. In the case of "polar" substances, molecular size, lipid solubility, and diffusibility are of minor importance; and the penetration depends upon the electro-chemical properties of the substances. Apparently negatively-charged acid compounds penetrate the barrier, while positively-charged basic compounds fail to do so. Colloidal substances do not penetrate, no matter what the charge. Thus tryparsamide, which penetrates well, is the sodium salt of an acid; and it circulates in the blood as a negatively-charged ion. Neoarsphenamide presumably also circulates in the anionic state; and sulpharsphenamide (which penetrates still more readily) is still more electro-negative in character. The diamidine compounds (e.g. diamidinostilbene) are salts of strong bases, and they circulate as positively-charged ions; but they do not penetrate into the cerebrospinal fluid. Suramin is an acidic compound, but it has a very large molecule and it probably circulates in a semi-colloidal form; as mentioned above, it does not penetrate into the fluid.

In attempting to correlate the electrochemical properties of substances with their power of penetrating vital membranes, it must be remembered that numerous other complicating factors are concerned in the animal organism. Thus the rate of disappearance and the rate of excretion must be considered. There is also the question of toxicity. In general, electro-negative substances are much less toxic than electro-positive compounds, and they remain longer in the circulation. However, while being less toxic for the host, they are often less lethal for the trypanosome. Tryparsamide owes its effectiveness to certain peculiar properties. It is relatively non-toxic, and in itself it has no trypanocidal action; it penetrates into the cerebrospinal fluid readily; perhaps all these properties are related to its electro-negative charge. After penetration, the arsenic atom (which it contains) is reduced from the pentavalent to the trivalent state; the properties of the molecule are radically changed and it becomes highly trypanocidal. By this means, reduced tryparsamide (which is extremely lethal to trypanosomes but which cannot, by its own nature, penetrate into the cerebrospinal fluid) becomes available for action at the desired place.

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299

EFFECTS OF NARCOTICS AND BENZEDRINE ON METABOLIC PROCESSES IN THE CENTRAL NERVOUS SYSTEM

by J. H. Quastel, *Transactions of the Faraday Society*, 39, 348-359, December 1943

In this contribution to the discussion from the Rothamsted Experimental Station of the *Agricultural Research Council*, the author reviews the evidence in favour of the hypothesis that narcotics intervene in an essential oxidative respiratory chain acting on a substrate which is mainly glucose.

In the past there has been a reluctance to relate narcosis with suppression of brain oxidations because of the disparity between the small quantity of narcotics required to produce narcosis, and the large amount needed to inhibit enzyme reactions. It is now realised that, since the pharmacological effect of the narcotic used is essentially localised, a large fall in the enzyme process of the entire tissue is not to be expected. It is established that the oxygen utilised by the brain is mainly concerned with combustion of glucose supplied by the blood, and any lack of glucose or oxygen results in slowing, then abolition, of cortical potentials with ultimate unconsciousness.

The observed facts are as follows:

i. In a series of seven barbiturates in a concentration of 0.12 %, inhibition of oxygen-uptake of minced guinea-pig brain in the presence of glucose is parallel to the increase in hypnotic activity.

ii. The parallelism extends to narcotics of widely different chemical structure, e.g. chloral, paraldehyde, hyoscine and atropine. Further, when a series of narcotics including ethylurethane, chloral hydrate, phenobarbitone, chlorbutol (chlorotone), hexobarbitone (evipan) and bromethol (avertin) is examined by the more sensitive brain-slice method, it is possible to show that the different narcotising concentrations of these compounds produce consistent inhibition of respiration of brain-cortex slices, and that this amount is approximately 15 %. This figure may be larger when localised centres are considered.

iii. The inhibition does not occur with all substrates; it is most marked with glucose, lactate and pyruvate, while succinate and *p*-phenylenediamine are undisturbed.

iv. The inhibition of oxidation of glucose, lactate and pyruvate by narcotics is seen in liver, kidney or diaphragm to about the same extent as in brain.

v. In low concentration the effect is reversible; high concentrations produce irreversible changes. Two effects are seen (a) in quick equilibrium between the narcotic and a respiratory system consistent with mass-action functions, occurring where the inhibition is not greater than 40 %, due to urethane, chloral, chlorotone, barbiturates, bromethol (avertin) and magnesium ions, and (b) a slow development of irreversible change with high concentrations of barbiturates or chlorbutol, and with low concentrations of ether, ethyl alcohol and indole.

vi. The steady state of the diminished respiration of brain slices produced by low narcotic concentrations of phenobarbitone or chlorotone depends on the concentration of K^+ in the medium. With concentrations of K^+ of 0.0128 M.—double that of normal serum—a steady inhibition is quickly obtained. At concentrations of 0.002 M. the respiration is found to drop in the presence of narcotics, at first more slowly, but finally to a very much lower level than the higher concentration of K^+ . When the temperature of the experiment, usually carried out at 39° C., is dropped to 29°, the variation is no longer appreciable.

vii. When the concentration of the substrate is increased eight-fold, no variation on the effect of inhibition of rat brain by chlorbutol is observed. This suggests that the narcotic enters into equilibrium with a component of the respiratory system and is independent of the substrate.

viii. A study of the inhibitory effect of chlorbutol on lactic dehydrogenase of minced brain tissue shows that there is

a simple competition for the enzyme, according to mass-action law, between narcotic and substrate. Contrasted to this is the finding that the narcotic inhibition of brain respiration is not due to inhibition of dehydrogenases affecting the glucose, lactate, or pyruvate. In addition, the inhibitive concentrations of narcotics do not affect the oxidation of sodium succinate or *p*-phenylenediamine. It is suggested that the explanation lies with the affinity of the narcotics for a special component of the aerobic respiratory system. Additional evidence that narcotics at low concentrations do not affect dehydrogenases arises in the observation that during anaerobic glycolysis by brain cortex no inhibition is seen.

ix. An examination of isolated and known tissue respiratory systems limits the effect of narcotic inhibition to a tissue component, possibly a flavoprotein.

The author goes on to discuss the possible connection between amine metabolism in the brain and the development of clinical narcolepsy, which is known to be relieved by amphetamine (benzedrine) administration. It is an experimental observation that the addition of amphetamine to brain slices in a glucose medium does not modify the respiration nor does it modify the diminution of respiration due to narcotics. Thus clinical narcolepsy and induced narcosis differ in this important respect. It is, however, shown that the addition of amphetamine to brain cortex respiring in tyramine and other inhibitive amines, neutralises the inhibition. Inhibition of brain respiration in the presence of tyramine is due to the oxidation of the amine to the aldehyde; amphetamine competes for the amine oxidase. Amines like *l*-ephedrine, triethylamine, triisopropylamine, hordenine and amphetamine are very feebly oxidised by amine oxidase and have a high affinity for the enzyme. They are therefore powerful inhibitors of amine oxidation.

300

RELATIONS BETWEEN *IN VIVO* AND *IN VITRO* ACTIONS OF CHEMOTHERAPEUTIC AGENTS

by H. McIlwain, *Transactions of the Faraday Society*, 39, 359-367, December 1943

Chemotherapeutic agents which act upon infections *in vivo* have often been tested to see if they also act upon the same bacterium or parasite *in vitro*. Sometimes such *in vitro* action has been found; in other cases, it has been absent because conversion of the drug by the host into an active form is necessary; again, in other cases it has not been found because the culture methods used to maintain the parasite *in vitro* were inadequate. The purpose of the present paper from the Department of Bacterial Chemistry of the Medical Research Council is to discuss the special conditions which must be observed in order that *in vitro* tests should yield reliable results.

The therapeutic effect of compounds such as sulphanilamide or acriflavine upon bacterial infections *in vivo* can be explained without showing that these drugs *kill* the bacteria *in vitro*; it is sufficient to show that they prevent multiplication of the bacteria (bacteriostatic action). If multiplication of the bacteria is prevented the host itself will usually kill the germs.

Prontosil rubrum is an example of a drug which is active *in vivo* but inactive *in vitro* because it requires conversion by the host into a more active form. In this case, the prontosil requires to be converted into the active sulphanilamide before its bacteriostatic effect can be demonstrated *in vitro*. Another example is the conversion of the pentavalent tryparsamide to its trivalent form in the body.

A different reason for failure to demonstrate chemotherapeutic action *in vitro*, occurred during the early history of the sulphonamides. In many studies, the bacteriostatic effect of sulphonamide could not be demonstrated in any bacteriological media *in vitro* because such media contained substances which prevented ("antagonised") the action of the sulphonamide; the most important of these substances or "antagonists" is now known to be *p*-aminobenzoic acid. This compound is similar in structure to sulphanilamide [*p*-aminobenzoic acid is a derivative of sulphanilamide] and its antagonism of the action of sulphonamides is due to the inhibition of enzymes by compounds which are structurally related to their substrates. This conception has been used by Fildes, and the

present author, as a clue to the designing of new chemotherapeutic agents. Thus pantoyltaurine, which is similar in structure to pantothenic acid, has been synthesized. Pantothenic acid is required for the growth of streptococci (*i.e.* it is an "essential metabolite"). When streptococci are exposed to pantoyltaurine *in vivo* or *in vitro* (provided there is no excessive amount of pantothenic acid present), the mechanism in the streptococci which utilises pantothenic acid is "blocked" by the pantoyltaurine, and growth of the organisms is thereby prevented. The amount of antagonist, *e.g.* *p*-aminobenzoic acid, required to inhibit the action of a drug, *e.g.* sulphanilamide, is often very different *in vivo* from that which is effective *in vitro*, because the tissues of the host may favour or handicap either the drug or the antagonist to different extents. Thus much more *p*-aminobenzoic acid is needed *in vivo* to antagonise the action of sulphanilamide than is needed *in vitro*, because *in vivo* much of the *p*-aminobenzoic acid is acetylated by the tissues and in this way it is inactivated. Again the action of a drug in one host may be much greater than it is in another host, because the level of antagonist in the body fluids may be much lower. Pantoyltaurine prevents the development of streptococci in rats; but it fails in mice, because the level of pantothenic acid (which antagonises pantoyltaurine) is much higher in the blood of mice than it is in rats.

Attempts have been made to correlate the therapeutic action of compounds with their effect upon the metabolism of parasites. Thus Fulton & Christophers (1938) [see also Christophers, 1943] showed that quinine and atebirin depressed the oxygen-consumption of malaria parasites. On the whole, however, such studies have not yet shown how chemotherapeutic compounds act or which enzyme mechanisms are concerned. At one time it was often suggested that compounds acted by stimulating the defence mechanisms of the host. The action of sulphonamides, acridines, and trypanocidal drugs upon phagocytosis and upon the production of antibodies has been studied in great detail, but no evidence can be found for this hypothesis. *In vitro* studies have also shown that other phenomena, such as drug-resistance and chemotherapeutic interference, depend entirely upon the interaction between drug and parasite, and that the participation of the host's tissues is not essential.

The author concludes by urging that much more attention should be paid to *in vitro* studies of the modes of action of chemotherapeutic agents. Most of the chemotherapeutic compounds which have been studied carefully have been found to exert a direct action upon the parasite (sometimes after preliminary conversion into a more active substance), and the hypothesis that any compound acts by stimulating the defence mechanisms of the host, rather than by direct action, would require great evidence in its support before it could be accepted.

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- ¹ [see BMB 297]

301

PHYSICO-CHEMICAL ASPECTS

by E. K. Rideal, *Transactions of the Faraday Society*, 39, 368-372, December 1943

Consideration of a simple biological process indicates several ways in which a drug may bring about modifications, such as by reaction with enzyme or co-enzyme, by altering the membrane permeability, or by changes in bulk media. Of the factors governing adsorption on to proteins, the part played by the hydrogen bond would appear to be important. Free energy data for the adsorption of dyestuffs on to wool show how the stability of the adsorbed molecule is determined by its polar and non-polar portions.

Studies, carried out by Professor Rideal's School at Cambridge, upon the structure and permeability of mono- and multi-layers, have clarified the early ideas of Traube and Overton, and thrown light upon the structure of membranes and upon the membrane factor in drug accessibility.

CHEMICAL CONSTITUTION AND PHARMACOLOGICAL ACTION

by H. R. Ing, *Transactions of the Faraday Society*, 39, 372–383, December 1943

The author, of *University College*, London, points out that, in a somewhat more general form than originally postulated by Ehrlich, the "receptor theory," despite its well-known limitations, does provide an otherwise missing intellectual link between the diverse concepts of structure and action. Our ignorance of the chemical nature of these hypothetical receptors forces us to look for relations between structure of the drug and the physiological effects presumed to flow from its receptor combination.

The organic chemist, using a known drug as a model, has found that related substances containing a particular structural feature ("pharmacodynamic group") often show similarity in action. The problem of apparent similarity in pharmacological activity shown by drugs of different structure would indicate, in the light of the receptor theory, that a closer analysis of such systems is required.

The opposite case, in particular the antagonistic action of drugs of similar structure, is interpreted on the basis that both drugs combine with the same receptors but that only one combination is physiologically effective.

With optically active compounds (e.g. adrenaline, hyoscyamine) the fact that they act additively suggests that the marked differences in activity depend upon the relative ease of combination with the receptors; with other stereoisomers differences may be ascribed to stereo-chemical effects.

With an homologous drug series the activity shows, in general, either a maximum or a regular increase in activity as the series is ascended. Despite the apparent simplicity of such systems it is concluded that this problem still awaits solution.

The need for further guidance from the physico-chemical standpoint was stressed by the author and several others during the ensuing discussion.

CHEMICAL STRUCTURE OF ARSENICALS AND DRUG RESISTANCE OF TRYPANOSOMES

by H. King, *Transactions of the Faraday Society*, 39, 383–389, December 1943

The early work of Ehrlich, Yorke, and their collaborators, showed that atoxyl-resistant strains were resistant to a great number of substituted derivatives of phenylarsonic acid as well as to the acridine group of dyestuffs.

From an extensive examination of a series of arsenicals the author of this paper, from the Chemistry Department of the *National Institute for Medical Research*, concludes that normal trypanosomes can be acted upon in at least three different ways.

The relatively low toxicity of compounds containing carboxyl groups, present as sodium salts, is ascribed to their unwillingness to leave the aqueous medium for the comparatively lipoidal trypanosome. Non-ionizable derivatives fall into two extreme classes and appear to act in at least two different ways. One type, exemplified by phenylarsenoxide, is active in similar high dilution upon normal and resistant strains alike, and this is ascribed to favourable adsorption at the liquid/water interface permitting facile transport to the site of action. The other type, e.g. benzamide *p*-arsenoxide, requires much higher concentrations and the lethal concentration-ratio for normal/resistant strain may be 32–64, suggesting adsorption on to polar surfaces which are present to a diminished extent in the resistant strain.

The author concludes with a brief discussion of the final mode of action of the toxophoric arsenoxide group. Reaction with —SH groups seems very likely.

An interesting point was raised by Dr. E. M. Lourie in the discussion. Since mepacrine, a quinine substitute, is an acridine compound, its use might produce arsenical-resistant strains of trypanosome, and this would be a serious matter since arsenicals are the only known effective remedies for the latest stages of sleeping-sickness. *In vivo* and *in vitro* experiments have shown, however, that this does not occur.

PRINCIPLES OF INSECTICIDAL ACTION AS A GUIDE TO DRUG REACTIVITY—PHASE DISTRIBUTION RELATIONSHIPS

by H. Hurst, *Transactions of the Faraday Society*, 39, 390–412, December 1943

In this paper from the Colloid Science Department, Cambridge and the *Imperial College of Science and Technology*, London, earlier theories of drug activity are considered in the light of data available from insecticidal studies.

A comparison of homologous fatty acids and alcohols shows that biological activity differs according to the site of application, e.g. internally in aqueous solution or externally as pure (liquid) drugs. A mixture of two non-toxic substances (e.g. ethyl alcohol and kerosene) may be extremely toxic, the phenomenon being termed "induced drug access." Such experiments show the importance of defining the nature and site of drug interaction.

The nature of the surface and framework of insect cuticle is discussed in relation to the mechanism of drug access and to the action of fat solvents and inert dusts. Inert powders appear to act by removal of lipid from the epicuticle surface. For the mechanism of drug access the experimental evidence suggests a two-dimensional surface diffusion along the interfaces of the lipo-protein mosaic.

The penetration of insect cuticle by fatty acids and alcohols, in terms of physico-chemical principles, is accorded a detailed treatment.

Using a related series of blowfly (*Calliphora*) larvæ with an homologous series of alcohols or fatty acids as drugs, the marked differences observed show that the biological activity of a given drug varies from system to system, as well as with the mode of application. Further complexities occur when other insects are used as test systems.

Solutions of pyrethrins in ethyl alcohol show, on addition of water, enhanced biological activity which can be ascribed to increased surface activity. The resistance of various insects suspended at an interface to monolayers of pyrethrins was found to be in the order of resistance to the drug when applied in an organic solvent.

The author concludes by reviewing pharmacological action in relation to fundamental biological pattern, showing the many points of resemblance between bounding membranes in such systems as insect cuticle, *Ascaris* integument, erythrocyte, and certain plant tissues.

The mechanism of two-dimension drug transmission in relation to the morphological arrangement of the insect cuticle was elaborated following a question on this subject by Professor Rideal.

SOME PHYSICAL-CHEMICAL PROPERTIES OF BIOLOGICALLY ACTIVE MOLECULES

by J. H. Schulman, *Transactions of the Faraday Society*, 39, 412–417, December 1943

The author, of the Colloid Science Department, Cambridge, refers principally to compounds containing both hydrophobic and hydrophilic groups, and proteins. He points out that, by means of the monolayer technique, the mutual interaction of two different molecules, when one or both are present at an interface, has been found to be determined by two components, one arising from the polar head-groups, the other from the van der Waals association of the non-polar "tails." For example, a soluble paraffin-chain salt interacts strongly, as shown by surface tension reduction, with monolayers of cholesterol, cetyl and elaidyl (*trans*) alcohols, but to a much reduced extent with oleyl (*cis*) alcohol owing to stereo-chemical hindrance. Such concepts must clearly be taken into consideration in any theory of drug action.

The adsorption of proteins on to charged monolayers of paraffin-chain compounds such as amines, acids, lecithin, cephalin, etc., at the oil/water interface can be demonstrated by means of oil/water emulsions. For example, an emulsion positively charged by means of a long chain amine will adsorb serum albumin only at pH > 4.6 (its iso-electric point)—i.e. when the protein is negatively charged. Such adsorption may completely remove biological activity (e.g. of bacterial toxins, snake venom, hormones), this returning when the emulsion is broken.

A POSSIBLE MODE OF ACTION OF BENZOPYRENE AS A TYPICAL CHEMICAL CARCINOGEN

by F. Weigert, *Transactions of the Faraday Society*, 39, 418-419, December 1943

This short paper is from the Physico-Chemical Department of the Mount Vernon Hospital, Middlesex.

The greater part of benzpyrene introduced into a mouse or rat is changed to non-fluorescent derivatives, about 1% is excreted unchanged, and the rest appears as the blue-fluorescent "BPX" in the bile and is excreted as 5-8-benzpyrene-quinone and as green-fluorescent "BPF" from which 8-hydroxy-benzpyrene has been isolated. From spectrographic and chromatographic examinations a tentative scheme for the metabolism is suggested, in which the intermediates fall into two groups (X- and F-) containing two different benzpyrene derivatives as prosthetic groups in combination with various cell constituents. Members of the X-group readily go over into the F-group.

"BPX" appears in just those tissues (skin, lung and liver) where benzpyrene produces tumours, suggesting that its instability and spontaneous transformation into "BPF" may provide the stimulus for the change of a normal into a malignant cell.

307

SOME MORPHOLOGICAL AND OTHER VARIATIONS IN A STRAIN OF *BACT. LACTIS AEROGENES* ACCOMPANYING ITS ADAPTATION TO CHANGE OF MEDIUM

by R. M. Lodge & C. N. Hinshelwood, *Transactions of the Faraday Society*, 39, 420-424, December 1943

This paper is from the Physical Chemistry Laboratory, Oxford. On repeated subculture in artificial media containing ammonium sulphate/amino acid mixtures as a source of nitrogen, some remarkable adaptation phenomena were found. For example, with ammonium sulphate alone the culture gave threads of almost indefinite length, cells of normal size being completely absent. The division function, the maximum population, and the initial lag-phase after inoculation, adapted themselves at different rates to a new medium, suggesting that these functions were independent.

308

THE EFFECTS OF RESORCINOL AND OF *m*-CRESOL ON THE GROWTH OF *BACT. LACTIS AEROGENES*

by G. H. Spray & R. M. Lodge, *Transactions of the Faraday Society*, 39, 424-431, December 1943

As reported in a previous paper¹ from the same laboratory, liquid artificial media were employed, and the effects of the two disinfectants on lags, growth-rates and stationary populations were determined. From the ways in which these characteristics of growth change with disinfectant concentration, the following conclusions were drawn:

i. Both compounds have specific actions on various stages of cellular metabolism in different ways.

ii. Inhibition of growth at the higher concentrations is due to indefinite prolongation of the lag rather than to reduction of the growth-rate or of the stationary population to zero.

iii. The effects of resorcinol can be completely neutralised by the bacteria during growth; with *m*-cresol only partial neutralisation occurs.

Thread-like cells are obtained at a certain concentration of *m*-cresol, using carefully controlled inocula. The theory that elongation and division are processes controlled by separate factors is applied to the experimental results.

¹ [see BMB 307]

309

THE ADAPTATION OF *BACT. LACTIS AEROGENES* TO GROWTH IN THE PRESENCE OF SULPHONAMIDES

by D. S. Davies & C. N. Hinshelwood, *Transactions of the Faraday Society*, 39, 431-444, December 1943

The authors, of the Physical Chemistry Laboratory, Oxford, chose sulphanilamide and sulphaguanidine as typical sul-

phonamide compounds. With increasing drug concentration the lag-phase is lengthened and the growth-rate is reduced, but never to zero, as in the case of certain other antiseptics.

In the presence of sulphonamide there may be a transition from a slower to a more rapid rate of multiplication at a certain stage during growth. This has been shown to be due to an adaptation of the bacteria.

Almost complete immunity is developed after thirty passages through sulphonamide-containing media. This immunity is not specific for the particular sulphonamide and is not reversible on passage through the normal medium. To explain why the growth-rate should be equal to that in sulphonamide-free media, the authors suggest that the cells develop enzymes which produce a sulphonamide antagonist. The adaptation is complex, the immunity developed after one or two passages through sulphonamide medium differing from that developed later, and is interpreted as the shortening of the lag of an alternative growth mechanism which is more resistant to sulphonamides than the normal one.

Antimalarials*

310

DRUG CONTROL OF MALARIA

by W. Hughes & F. Murgatroyd, *Lancet*, 1, 699-704, 5/6/43

The loss of Java deprived the United Nations of 90% of the world's normal sources of quinine. The total alkaloids of cinchona bark from South America will probably form a substitute as effective as quinine itself, but the greatly increased need for antimalarial drugs makes it necessary to have a sufficient supply of an alternative drug. Mepacrine (atebrin) is the only synthetic compound of any real value at present in general use, and measures have been taken to meet all expected demands for it.

Treatment of clinical attacks. The extensive studies of Stephens and others (1917, 1919, 1923) on the treatment of malaria, and later work on the treatment of general paralysis by induced malaria (League of Nations Malaria Commission, 1933) have shown that the most intensive treatment was little superior to moderate dosage either in acute attacks or in preventing relapses. In *P. vivax* infections, relapses tend to occur about the second and eighth month after the primary attack and in *P. falciparum* infections mostly within two months after the primary attack.

The final cure of infection is probably effected by an immunological process, and its development appears to be obstructed by too early or too intensive treatment with drugs which probably deprive the body of antigen needed to stimulate the formation of antibodies. The treatment which is suitable for the poverty-stricken populations of malaria zones is different from that for Europeans, such as troops, who are exposed to infection for limited periods only. In the former the development of immunity is important and the League of Nations Commission (1937) suggested 15 grains of quinine [1 g.] daily for 7 days in acute attacks, with larger doses in severe cases. In the case of Europeans, the cost of treatment and the development of lasting immunity are less important. For an acute attack 10 grains of quinine or 0.1 g. of mepacrine (atebrin) thrice daily for 5 or 6 days is usually sufficient; the addition of pamaquin (plasmochin), e.g. 0.01 g. twice or thrice daily for 5 days, is believed to lessen the tendency to relapse in *vivax* infections, but it is less clear whether it does so in *falciparum* infections. Anti-relapse courses which have been recommended are:

- i. Quinine 10 grains or mepacrine 0.1 g. twice or thrice daily on 2 consecutive days of each week for 2 months after the treatment of the primary attack.
- ii. The normal suppressive (prophylactic) dose daily for 2 months.
- iii. Mepacrine 0.1 g. thrice daily for 5 days beginning 10 days after the treatment of the acute attack has ended.

In the acute attack some prefer to combine all three drugs, e.g. quinine for 2 or 3 days, then mepacrine for 5 days, and finally pamaquin.

* [see also BMB 297 & 343]

The authors are not convinced by the claims of some advocates of intensive treatment (Murray & Shute, 1942; Hill, 1942; Bryant, 1942). Apart from the question of the greater effectiveness of large doses, the possible occurrence of toxic symptoms or other unpleasant effects must be considered. Some of the apparent failures of moderate doses have been due to defective administration of the drug, e.g. in persistent vomiting when the drug should have been given parenterally, or to defective quality of the drug used. Such reasons probably explain also the failures attributed to the presence of drug-fast parasites.

Suppressive treatment. No known drug will certainly prevent malarial infection, but the clinical effects of the infection may be prevented or modified. There are several satisfactory reports of the use of mepacrine in suppressive treatment. Daily doses of 0.05 g. to 0.1 g. for several months, even up to 2 years, have been successful. In well-controlled trials in Malaya a weekly dose of 0.3 g. was found to be satisfactory (Niven, 1938; Field, 1939). The League of Nations Malaria Commission (1937) thought that 0.05 g. mepacrine daily was slightly inferior, and 0.2 g. bi-weekly slightly superior to 5 grains of quinine daily. Hill (1942) found 0.1 g. mepacrine daily for some months to be effective and without toxic effects. Recently a dose of 0.1 g. mepacrine for 6 days of each week has been recommended for persons in a hyperendemic area, beginning a week before entering the area and continuing for a week after leaving it.

Problems in diagnosis. In a hyperendemic area it is usually impossible to distinguish relapses from reinfections and this is important in estimating the value of treatment. When routine suppressive treatment has been taken by non-natives, parasites may be difficult to find, but they are nearly always present in severe clinical cases. The presence of malarial parasites in the blood of natives is of course less significant. Cases classed as chronic malaria or malarial cachexia are sometimes difficult to diagnose, and there is some difference of opinion as to whether it is safe and advisable to withhold drugs for some days in order to allow the parasites, if present, to become evident, or to give curative doses at once.

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311

EFFECTS OF PLASMOQUIN, ATEBRIN, AND QUININE ON THE ELECTROCARDIOGRAM

by H. L. Heimann & B. G. Shapiro, *British Heart Journal*, 5, 131-133, July 1943

Electrocardiograms of a soldier who had complained of præcordial pain during treatment of malaria with plasmoquin showed changes similar to those of coronary disease. The clinical features did not support such a diagnosis, however, and in order to ascertain whether the effect could have been produced by plasmoquin an investigation on convalescent soldiers was carried out.

Six men convalescing from malaria were due to receive prophylactic medication against recurrences. After preliminary cardiograms, the men received pamaquin (plasmoquin) $\frac{1}{2}$ grain [about 10 mg.] twice daily for 7 days. Cardiograms were repeated, and the men had a week's rest. They then received mepacrine (atebrin) 1.5 grains [about 0.1 g.] three times a day for a week, and cardiograms were repeated once more. They were then given 5-10 grains [about 0.3-0.6 g.] quinine for 6 days and a final cardiogram was taken. The observations were made on the chest leads IV R and IV F.

The authors concluded that pamaquin increases the amplitude of the various deflections, particularly the T wave. In some cases there was elevation of the S-T segment similar to that of coronary thrombosis. Mepacrine decreased the amplitude of the deflections, particularly the T wave. It restored the S-T elevation produced by pamaquin. Quinine produced changes similar to but less striking than those produced by mepacrine.

312

THE ACTIVITY OF DRUGS IN THE MALARIA OF MAN, MONKEYS AND BIRDS

by F. H. S. Curd, *Annals of Tropical Medicine and Parasitology*, 37, 115-143, September 1943

The only practicable large-scale method of testing drugs for antimalarial action is by the use of experimentally inoculated birds. The malarial parasite usually employed is *Plasmodium relictum*. However, the plasmodia responsible for human malaria show qualitative differences in drug-susceptibility, and there is evidence of varied response to drugs on the part of the parasites responsible for monkey and avian malaria. Little is known of variations in response by different strains of the same species.

If the search for antiplasmodial activity in drugs is limited to one species or one strain of avian malaria, there is a possibility that important information on the relation of chemical structure to therapeutic action may be missed.

The author, of the Research Laboratories of *Imperial Chemical (Pharmaceuticals), Ltd.*, Manchester, believes that investigations on different species and strains of plasmodia will be necessary in the future, and with a view to facilitating these he has compiled a table showing the actions of various drugs in different malarias (excluding the established antimalarial drugs in the 3 types of human malaria). The table occupies 16 pages of this paper, and is based on a search of the literature from 1914 (a few outstanding older papers have been included). A list of 277 references is appended.

313

THE ACTION ON AVIAN MALARIA OF THE ALKALOIDS OF CINCHONAS FROM THE CAMEROONS AND THE BELGIAN CONGO

by P. Baranger & P. E. Thomas, *Biochemical Journal*, 37, 342-344, September 1943

In this paper from the *Centre de Technologie Scientifique et Coloniale de la France Combattante*, Finedon, England, the authors, the first of whom was formerly professor at l'École Polytechnique, Paris, summarise the results of tests of the antimalarial value of cinchona barks from the French Cameroons and the Belgian Congo.

Total alkaloids from *C. succirubra* and *C. Ledgeriana* exerted an effect similar to that of quinine in retarding the onset of avian malaria. Results with total alkaloids from which the quinine had been extracted were poor.

The alkaloids were administered orally as pellets, and birds (canaries) were inoculated with a strain of *Plasmodium relictum* obtained from Professor Keilin of Cambridge. The paper contains 22 references to the relevant literature, and a tabulation of the results of the authors' investigations.

314

UNIMPAIRED SUSCEPTIBILITY OF *TRYPANOSOMA RHODESIENSE* TO ARSENICALS AFTER INTENSIVE TREATMENT BY MEPACRINE

by E. M. Lourie & H. O. J. Collier, *Annals of Tropical Medicine and Parasitology*, 37, 205-210, December 1943

It has long been known that sub-curative doses of arsenic may produce resistance in pathogenic trypanosomes to non-arsenical trypanocidal dyes of the acridine and related groups. Arsenic-resistance may also be produced by non-arsenicals.

Mepacrine (atebrin, quinacrine) is an acridine derivative, and in view of the increased use of this synthetic antimalarial in Africa it is important to know whether it produces arsenic-resistance in trypanosomes (which might prevent effective treatment of sleeping sickness).

Experiments, which are recorded in detail in this paper, showed that intensive *in vivo* and *in vitro* exposure of *Trypanosoma rhodesiense* to mepacrine did not produce arsenic- or mepacrine-resistance. The authors conclude that mepacrine is suitable for use in sleeping sickness areas.

Non-Arsenical Trypanocides*

315

THE PHARMACOLOGICAL ACTIONS OF CERTAIN AROMATIC DIAMIDINES POSSESSING TRYPANOCIDAL ACTIVITY

by R. Wien, *Annals of Tropical Medicine and Parasitology*, 37, 1-18, April 1943

The pharmacological activity of four aromatic diamidines, pentamidine (4 : 4'-diamidino 1 : 5 diphenoxypentane), phenamidine (4 : 4'-diamidino diphenyl ether), propamidine (4 : 4'-diamidino 1 : 3 diphenoxypropane) and stilbamidine (4 : 4'-diamidino stilbene), was investigated in the biological laboratory of *May & Baker Ltd.* The toxicity of these substances was studied in mice, rats and rabbits and their action on the vascular system, heart, respiration, central nervous system, smooth muscle, and striped muscle was also determined.

Phenamidine proved to be the least toxic of the four substances, but their toxicities were all quite similar. The average lethal doses ($L.D_{50}$) for mice by intravenous injection were: phenamidine 0.050, stilbamidine 0.031, propamidine 0.02 and pentamidine 0.028 mg. per g., and by subcutaneous injection, 0.120, 0.180, 0.055 and 0.064 mg. per g. respectively. All four compounds caused general depression of the central nervous system; respiration was first accelerated and then became slow and forced. There was slight ataxia in the hind limbs, and the rectal temperature was lowered. Death was due to respiratory failure. The effects of the diamidines on rabbits were very similar.

To investigate possible cumulative action, pentamidine and stilbamidine were given to rats by subcutaneous injection daily for 10 days in doses of $\frac{1}{10}$, $\frac{1}{5}$ and $\frac{1}{2}$ of the average lethal doses as found in mice. With $\frac{1}{10}$ of the average lethal dose there was no evidence of a cumulative effect, but with $\frac{1}{5}$ and $\frac{1}{2}$ of the average lethal doses, both showed a definite cumulative action, indicated by retardation of the growth of the animals. The site of injection was inflamed after 5 days in some cases and toxic effects were observed at this time.

All four diamidines caused a marked fall in blood-pressure in anaesthetised or decerebrate cats, but if the injections followed each other too rapidly, the response was not uniform and usually the depressor effect decreased. Doses of 1 mg. usually produced an effect, but phenamidine was less active than the other compounds. Full doses of atropine reduced, but did not abolish, the effects. The amidines were also found to have a depressor action in eviscerated preparations and in the "spinal" cat. The previous injection of calcium chloride or gluconate in an anaesthetised cat had the effect of reducing the fall in blood-pressure due to the administration of the diamidines. The decrease in blood-pressure was shown by the plethysmograph results to be due to general vasodilatation, and it was also demonstrated that the effect was peripheral and not central in origin. It was not due to direct depression of the heart, for in concentrations of about 1 : 2,000 the diamidines increased the rate and force of the beat of the isolated heart of the cat and rabbit, though in concentrations of about 1 : 200 a slight transitory depressant effect was observed.

When large doses of the diamidines were given to rabbits for several days, the effect on respiration was one of general depression. In decerebrate cats, the effect of doses which caused a fall in blood-pressure was an increase in depth and volume of respiration, with little influence on the rate.

In the intact animal little or no stimulation of the central nervous system was observed, as indicated by the absence of convulsions and by the depressant effect on the respiratory centre. The acute effect of these compounds on the central nervous system was studied in a special patellar reflex preparation in the cat, but no influence on this reflex was observed.

In concentrations of 1 : 10,000 to 1 : 25,000, the diamidines

stimulated the smooth muscle of isolated rabbit intestine, both tonus and movements being increased. The substances had no marked direct effect on the isolated guinea-pig ileum, but modified the contractions produced by histamine. In concentrations of about 1 : 16,000, they caused contraction of the relaxed muscle of the isolated guinea-pig and cat uteri, but not in the uterus of the intact animal. There was no appreciable effect on the isolated rabbit uterus.

The effect of the diamidines on the excitability of nerve-fibres and muscle was also studied and it was shown that these substances sensitised muscle to the action of potassium ions, though if the concentration of the diamidines exceeded 1 : 5,000, they themselves caused contraction of the muscle.

With these four diamidines, the effects on blood-pressure and intestine were more or less parallel with the toxicity, the least toxic having the least effect on pressure and intestine. The fall in pressure was only partially explained by stimulation of the parasympathetic system, and was not due to any impairment of the action of the heart, but chiefly to vasodilatation of peripheral origin, taking place in the skin and muscles. A characteristic effect of the diamidines was an ergotamine-like action in antagonising the action of adrenaline.

316

THE METABOLIC EFFECTS PRODUCED BY CERTAIN AROMATIC DIAMIDINES

by R. Wien, W. Freeman & N. M. Scotcher, *Annals of Tropical Medicine and Parasitology*, 37, 19-33, April 1943

In this paper are described the effects of the four aromatic diamidines, pentamidine, phenamidine, propamidine and stilbamidine, on carbohydrate metabolism, calcium and potassium metabolism, and on the blood-picture, the kidneys and the liver. The animals used were rats, guinea-pigs, rabbits and dogs. The diamidines were used in the form of their isethionate salts, which are more soluble than the hydrochlorides, and the injections were given intravenously and subcutaneously to rabbits, subcutaneously to rats, intramuscularly to guinea-pigs, and intravenously to dogs.

Phenamidine did not affect the blood-sugar level to any great extent; doses of 10 and 15 mg. per kg. given intravenously to rabbits had little effect, but 20 mg. per kg. caused a delayed hyperglycaemic response. Stilbamidine was hyperglycaemic, but only in doses which were almost lethal. In some, but not all experiments, propamidine given subcutaneously had a marked hyperglycaemic effect. When administered intravenously, lower doses caused a fall in blood-sugar, while higher doses brought about an initial hyperglycaemia, followed later by fatal hypoglycaemia. Propamidine was the only one of the four diamidines studied which showed a hypoglycaemic action. Pentamidine was hyperglycaemic in doses not far from the lethal amounts. Stilbamidine, the only compound tested in this way, was shown to reduce the hyperglycaemic action of adrenaline. The adrenals were found to play some part in the effect of stilbamidine and propamidine on the blood-sugar.

No depletion in liver glycogen was observed a short time after a single administration of diamidines, but there was depletion after four injections, given on alternate days, though this may have been due to the anorexia which the animals developed.

When large doses were given intravenously to rabbits, phenamidine and especially propamidine had a marked effect on kidney function; the blood-urea and non-protein nitrogen rose to a high level within 24-48 hours and remained there for at least 5 days. The other two diamidines caused only a slight increase within 7 hours, disappearing within 2 days. Similar results were obtained with subcutaneous injections, though, by this route, phenamidine was less toxic than stilbamidine, while propamidine and pentamidine were more toxic.

In both dogs and rabbits the diamidines were found to produce a slight fall in the concentrations of calcium and potassium in the blood-serum. In dogs the fall was about the same for calcium as for potassium, but in rabbits the fall in potassium was the greater, so that the calcium-potassium ratio was increased.

Repeated administration of therapeutic doses of stilbamidine and propamidine to guinea-pigs had no effect on the blood-picture, other than leucocytosis and increase in polymorphonuclear cells before death when toxic doses were employed.

* [see also *BMB* 298 & 337]

Stilbamidine and propamidine were given daily for 5 days to guinea-pigs by intramuscular injection, and histological examinations of the liver and kidneys were then made. There were no changes in the kidneys, even with the higher doses, except for slight cloudy swelling. The most important pathological effect of the substances in toxic amounts was extensive fatty degeneration of the liver, but this was not observed with repeated administration of therapeutic doses.

317

A COMPARISON OF THE BIOLOGICAL ACTION OF BAYER 7602(Ac) AND THE CORRESPONDING I.C.I. SYNTHETIC PRODUCT

by J. D. Fulton, *Annals of Tropical Medicine and Parasitology*, 37, 164-173, December 1943

In 1937, Iensch described the preparation of a new compound in the 4-amino-quinoline series which was subsequently known as Bayer 7602(Ac). It was stated to be active against *Trypanosoma cruzi*, but not against other trypanosomes. Mazza and collaborators tried the compound clinically in Chagas's disease, recently described (Mazza, Basso & Basso, 1942) its successful employment over a period of 5 years, and compared it with a new compound, Bayer 9736(As), which is less toxic, less active against *T. cruzi*, but also acts on a number of other trypanosomes.

Because supplies of Bayer 7602(Ac) ceased to reach South America, Imperial Chemical Industries Limited undertook to prepare the compound. The present paper, by a member of the scientific staff of the Medical Research Council, describes comparative tests on mice inoculated with *T. cruzi* of the German and British products.

Full details of the experimental procedures are given. The conclusions were that (i) both preparations freed the peripheral blood of parasites, (ii) tissue forms of the parasite seemed to be inaccessible, (iii) in no case was cure of the infection obtained, (iv) the compound had little value as a prophylactic, (v) no significant difference was found in the biological actions of the British and German preparations.

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Sulphonamides*

318

THE LOCAL ACTION OF SULPHONAMIDES

by F. Hawking, *Practitioner*, 151, 354-361, December 1943

Although sulphonamides were first introduced into medicine in 1935, their use for local application did not become firmly established until 1940, when Colebrook & Francis (1941) showed that wounds infected with hæmolytic streptococci could be freed from these organisms by sprinkling them with sulphanilamide. During the three years which have elapsed since then, much experience has been gained.

Choice of compound. For use as a local application to wounds, there are only two compounds to be considered—sulphanilamide and sulphathiazole. Sulphadiazine has been suggested for this purpose, but it is less soluble, less active, and less plentiful than sulphathiazole, and it has no counterbalancing advantages. As regards the two first mentioned, sulphanilamide is less active against bacteria but is more than ten times as soluble (1,970 mg. per 100 cm.³ serum at 37° C.) as sulphathiazole, and its concentration can therefore be ten times as great. In addition, it is plentiful and can be used freely. It is quickly absorbed from the wound so that there is little danger of leaving insoluble deposits, but on the other hand it hardly stays in the wound long enough to obtain the best results. Sulphathiazole is much more active (10-100 times) *in vitro* than sulphanilamide, but is less soluble (190 mg. per 100 cm.³ serum at 37° C.) and more expensive. It persists longer in a wound and so inhibits bacteria for a longer period; this persistence in the wound is a valuable asset. As used in a wound, the toxicities of both compounds for the neighbouring tissues are about equal. Weight for weight, sulphathiazole is more toxic for cells than sulphanilamide,

but since it is less soluble the concentration is much lower. As each compound has merits and demerits, it is advantageous to combine them by using a mixture of one part sulphathiazole with two or three parts of sulphanilamide.

Diffusion through a wound. When a sulphonamide compound is placed in a wound, its distribution round the wound depends upon the physical factors of solubility, diffusion, etc. There are four places to consider:

i. The main cavity of the wound: The concentration in the wound fluid next to the deposit of sulphonamide depends upon the solubility. Thus the concentration of sulphanilamide will be about 2,000 mg. and that of sulphathiazole about 190 mg. per 100 cm.³.

ii. Crevices of the wound: From the fluid near the deposit of sulphonamide, the compound spreads outwards by convection currents and by diffusion. Convection currents ought to be minimal in a wound at rest and those which do occur will be from the deeper parts to the surface, so they will be a hindrance rather than a help. Diffusion is rapid over short distances, such as from one side of a cell to another, but it is very slow over the longer distances such as occur in wounds, as the time required is proportional to the square of the distance. At the end of one hour, an appreciable concentration of sulphanilamide, e.g. 1 mg. per 100 cm.³, does not spread further than 1 cm., and after 24 hours it does not travel more than 4.5 cm. For sulphathiazole, the distances travelled are only two-thirds of these. Accordingly, sulphonamide placed on the surface of a wound does not penetrate deeply by its own power. Surface application is sufficient for superficial injuries such as burns, but in order to reach the deeper parts, the compound must be mechanically distributed over the whole wound as widely as is reasonably possible.

iii. Dead tissue adjacent to a wound: Penetration of dead tissue occurs by the same process of diffusion as above, and it is similarly slow. Hawking (1941b) showed that it took 6 hours or more for sulphanilamide or sulphathiazole to pass through a sheet of tissue 3 mm. thick in appreciable, but still very small, amounts.

iv. Living tissue adjacent to a wound: Before the compound has penetrated very far, it meets a capillary and it is swept away into the general circulation; the concentration in living tissue near a wound is therefore no greater than that in the blood generally. The best way to reach such tissue is to give the compound by mouth or intravenously.

Rate of absorption from wounds. Sulphanilamide is absorbed from wounds rapidly, especially from large burns, and excessive amounts placed in or on a wound may cause toxic symptoms such as cyanosis, nausea, or even coma. In the treatment of burns among British troops in Egypt, several deaths were caused in this way before the danger had been fully realised. As a rough approximation, absorption from a wound is about half as rapid as that from the alimentary canal; and a maximal blood concentration of 1 mg. per 100 cm.³ will be produced for each 1 to 2 g. sulphanilamide inserted into the wound. In view of this rapid absorption, 10 g. sulphanilamide is enough for most wounds, and the total amount used in any one patient should rarely exceed 15 g. Sulphathiazole is absorbed more slowly and there is much less danger of toxic effects.

Antagonising substances. Unfortunately the antibacterial action of sulphonamides in a wound is often antagonised by substances derived from necrotic tissue and pus, which act in the same way as *p*-aminobenzoic acid. Consequently pus and necrotic tissue should be removed from the wound as completely as practicable before the sulphonamide is inserted.

Effect upon wound healing. Very much work, both experimental and clinical, has been done to determine whether sulphonamides have an injurious effect upon the healing of a wound. It is the general conclusion that sulphanilamide does have a slight but definite adverse effect upon a clean wound (as is shown clinically by the presence of a little serous exudate and by slight delay in closing), and that in such wounds it is possibly better not to use it. But in infected wounds, the effect of sulphanilamide upon the tissues is negligible compared with the much greater harm which bacteria would cause if sulphanilamide were not used. In particular, sulphonamides do not interfere with phagocytosis. However, sulphanilamide should not be placed near large nerve trunks, as it may cause degeneration (Holmes & Medawar, 1942); and sodium sulphathiazole and other

* [see also *BMB* 341 & 300]

sodium salts should not be used as they are strongly alkaline and cause necrosis.

Therapeutic effect in experimental wounds. As statistics about the value of sulphonamides in preventing infection of human wounds are difficult to obtain, much of the evidence is derived from experimental wounds in animals. Thus in a series of guinea-pig wounds, infected with over 10,000 lethal doses of gas gangrene organisms, the local application of sulphanilamide saved 53 % of those infected with *Cl. welchii* but none of those infected with *Cl. septicum*; sulphathiazole saved 67 % of those infected with *Cl. welchii* and 75 % of those infected with *Cl. septicum*; in the case of infections with *Cl. œdematiens* (novyi), none of the sulphonamides was of much value (Hawking, 1941a). In a series of wounds in rabbits infected with hæmolytic streptococci, plain sulphanilamide saved only 2 out of 14 animals, because the drug was absorbed from the wound too quickly. Oily preparations of sulphanilamide, in which absorption was delayed, saved 12 out of 20, but the oil which remained embedded in the tissues caused very undesirable fibrosis and other reactions (especially cod liver oil). Sulphathiazole saved 10 out of 10 animals, partly because it was more actively bacteriostatic and partly because it persisted for a longer time in the wound (Hawking, 1942).

Extent of local application in clinical practice. Prophylactically sulphanilamide is applied to wounds and burns in the field, and it is sprinkled into wounds after operation to prevent anticipated infection. In general, clinical impressions of this treatment are favourable. For the treatment of burns of the face and limbs in the armies in North Africa, where such lesions formed one of the major groups of casualties, sulphanilamide plus vaseline gauze supplanted all other methods of treatment in the forward areas. Curatively, sulphonamides are applied to wounds which are already infected. Hæmolytic streptococci are usually suppressed by this means, but sometimes resistant strains occur or develop. *Proteus*, *Ps. pyocyanea* and many strains of staphylococci are insensitive. The treatment has been found particularly valuable in preparing superficial wounds for skin grafting.

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¹ Hawking, F. (1942) *Lancet*, 2, 507
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¹ [see BMB 51] ² [see BMB 21] ³ [see BMB 126]

319

A STUDY OF THE DISTRIBUTION OF SULPHANILAMIDE

by F. Alexander, *Quarterly Journal of Experimental Physiology*, 32, 21-28, May 1943

The author, working in the Department of Pharmacology, Edinburgh University, investigated the distribution of sulphanilamide in sheep, rabbits and mice, in all of which acetylation occurs, as in man. After the intravenous injection of a suitable amount of the compound, measurements were made of the blood concentration and of the amount excreted in the urine; after suitable intervals, the smaller animals (rabbits and mice) were killed, and the sulphanilamide content of the tissues was estimated.

When sulphanilamide (40 to 90 mg. per kg.) was given to sheep or rabbits, the blood concentration after 1 hour was the same as, or slightly higher than, it would have been if the sulphanilamide was evenly distributed throughout the body, but at 6 hours it fell below this amount, and after 24 hours it was much less than the theoretical amount, showing that either the drug was not evenly distributed through the body water, or it had been removed from estimation by some chemical change. This conclusion was strengthened by measurement of the amount excreted in the urine. After doses of about 1 to 2 g. for sheep weighing about 20 kg., or of 0.1 g. to rabbits weighing about 1.5 kg., the total amount excreted in the urine was only 40-80 %.

A search was then made to see whether the sulphanilamide which had disappeared had been fixed in the tissues. Rabbits were given 3.5 to 7.5 mg. per 100 g.; they were killed at

intervals, and the tissues were examined chemically. The concentration in the liver and kidney was higher than that in the blood; the concentration in the kidney was particularly high in the first six hours, presumably due to excretion into the urine. It was found that the amount retained in the tissues was too small to account for all the drug which had been lost. This point was tested further by injecting a solution of sulphanilamide into mice, and measuring the amount in the excreta and the amount in the complete animal, killed and estimated as a whole. The results are shown in the table:

The Percentage of Dose recovered from the Whole Animal and Excreta

Time, hrs.	No. of observations	Percentage recovered			Percentage destroyed
		Body	Excreta	Total	
0	9	92.2	0.0	92.2	7.8
$\frac{1}{2}$	13	84.5	3.2	88.0	12.0
$1\frac{1}{2}$	7	62.0	17.6	79.4	20.6
3	8	31.6	33.2	65.0	35.0
24	7	8.5	62.4	70.9	29.1
48	5	6.7	61.0	67.7	32.3

Clearly, about 30 % of the sulphanilamide injected is converted into some form which cannot be detected by the standard method of Bratton & Marshall (1939), even after acid hydrolysis; this conversion would almost certainly destroy all its therapeutic action. The apparent discrepancy between these results and those of Marshall, Emerson & Cutting (1937) is probably explained by the fact that these workers administered the drug orally, so that 2 hours would be occupied by absorption, and they examined the tissues at 4 hours, which would correspond to only 2 hours after intravenous injection, at which time the loss is still small.

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320

THE EFFECT OF ACID, ALKALI, AND MEALS ON THE BLOOD LEVEL AND EXCRETION OF SULPHAPYRIDINE IN CHILDREN

by H. E. C. Wilson, *British Medical Journal*, 1, 507-508, 24/4/43

Alkali is often given to patients receiving sulphonamide compounds, in order to combat acidosis or to prevent precipitation of crystals in the urinary passages. The present author, who is Biochemist to the *Royal Hospital for Sick Children* at Glasgow, has investigated the effect of this practice upon the absorption and excretion of sulphapyridine.

His observations were made on 15 children suffering from non-relevant conditions, e.g. chorea. The test consisted of giving a single dose of sulphapyridine, 50 mg. per kg. body weight, and measuring the urinary excretion during 24 hours and the blood concentration after 1, 4, and 8 hours. Three separate tests were carried out on each case: (i) sulphapyridine alone, (ii) sulphapyridine plus 2 g. sodium bicarbonate, (iii) sulphapyridine plus 1.3 g. ammonium chloride. The individual figures obtained varied greatly, but on taking an average it was found that the addition of acid or alkali to the sulphapyridine had no effect upon the subsequent blood concentration (4.1 mg. per 100 cm³. at 1 hour, 5.2 mg. at 4 hours, and 4.6 mg. at 8 hours), or on the rate of excretion (50 % of the dose was excreted in the urine in 24 hours, of which 52 % was present as free sulphapyridine). There was no correlation between the giving of acid or alkali and the frequency of vomiting.

In a second series of cases, a study was made of the effect of taking the drug two hours before a meal as compared with taking it two hours after. The time of the meal had no effect upon the rate of absorption of the compound. The excretion of the drug was slightly greater if the drug was taken immediately after a meal; but although this effect was large enough

to be statistically significant, it was not sufficiently great to be of any practical clinical importance. The author concludes that for clinical purposes the giving of acid or alkali, or the adjustment of the dose in relation to meals, has no practical effect upon the rate of absorption or excretion of sulphapyridine.

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321

SULPHAPYRIDINE ABSORPTION THROUGH THE HUMAN PLEURA

by H. E. Vickers, *Lancet*, 2, 760-762, 18/12/43

An account is given of the absorption of sulphapyridine through the pleura, as observed in 22 cases. The drug was placed in the pleural cavity as a powder (usually 7.5 g.) at the end of operation, and was spread over the pleura immediately before the operation wound was closed. Morning and evening estimations of the amount of free sulphapyridine in the blood were then made until the amount present was less than 0.5 mg. per 100 cm.³. No sulphonamides were given by mouth during this time. In all but two cases the maximum level was attained within 24 hours of application. The highest maximum recorded was 5.5 mg. per 100 cm.³, and the lowest 1.0 mg. The time taken to eliminate the drug varied from 3 to 9 (average 6) days, and the rate of elimination was fairly constant in each case. The pleural fluid and the blood levels of the drug were not closely related. Absorption of sulphapyridine through the pleura varies considerably in different cases, as judged by relative sulphapyridine concentrations in the pleural fluid and blood at the same interval after application. This is probably due to caking of the powdered drug and the formation of pleural adhesions which interfere with free absorption.

322

SULPHONAMIDE DERMATITIS: SENSITISATION FROM LOCAL APPLICATION

by B. C. Tate & I. Klorfajn, *Lancet*, 1, 39-44, 8/1/44

Although most of the toxic reactions to internal administration of the sulphonamides are now well known, ill effects from their external use are less generally recognised. Apart from a warning by Ingram (1942) that the local application of these drugs may cause sensitisation, the present writers found no mention of such effects in the literature. In their own experience sensitisation occurred in an appreciable proportion of cases. In those affected, an irritating eczematous dermatitis appeared after a period of sulphonamide application; it was at first confined to the area under treatment, but it usually spread to other regions. This "secondary eruption" usually had the distribution commonly seen in sensitisation to other chemicals. Exposure to sunlight facilitated dermatitis and there is evidence that sulphonamides themselves can cause sensitisation to sunlight. It was difficult to assess the number of applications of sulphonamide dressings necessary to cause sensitisation. In 30 cases about which fairly accurate data were available, the interval between the first application of sulphonamide and the appearance of the eruption varied between 4 and 14 days in 21 cases, and was more than 14 days in the remaining 9 cases. The nature of the original disease is an important factor in the development of sensitisation; of 55 cases, 15 had been treated for impetigo and 12 for ecthyma. On the other hand, it does not seem that any recognisable constitutional predisposition is necessary for the development of sensitisation.

It appears that no single sulphonamide preparation is more likely than any other to cause dermatitis. Patients sensitised to one of the sulphonamide drugs are thereafter sensitive to other members of the group. Sensitisation is probably permanent; in 3 patients examined by the authors sensitivity had persisted for 18, 15 and 6 months respectively.

Treatment of the weeping areas of the dermatitis with Lassar's paste dressings was effective, and a lead and calamine lotion was applied to dry parts of the rash. Desensitisation was attempted and was apparently achieved in 3 cases; these

were given sulphanilamide orally, 1 g. three times daily for 8 days. Ten other patients were later successfully desensitised by this method, but whether such desensitisation will be permanent or whether the method is universally applicable is not yet known.

The authors point out that sensitisation to sulphonamides resulted from treatment of conditions for which equally efficient, if not better, alternative remedies are available; it may be as intense as to preclude subsequent administration of these drugs in effective doses for other diseases. For this reason local sulphonamide therapy for skin diseases and minor injuries is unjustifiable and should be discontinued. The original paper contains 11 photographs illustrating the skin eruptions seen.

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323

CHEMOTHERAPY AND SEROTHERAPY IN CEREBROSPINAL (MENINGOCOCCAL) MENINGITIS: An Analysis of 3,206 Case Reports

by A. A. Jubb, *British Medical Journal*, 1, 501-504, 24/4/43

This paper, by a Medical Officer of the British Ministry of Health, opens with a summary of the incidence of cerebrospinal fever in England and Wales from 1913 to 1940 and of the results of treatment in that period by anti-meningococcal serum, and proceeds to an analysis of recent results of treatment by chemotherapy (sulphonamide derivatives) combined with serum and by chemotherapy alone. During the severe epidemic in 1940 the Ministry of Health made arrangements for the collection of information on the results of those methods of treatment. Special forms were provided showing the nature of the particulars desired, and were supplied to large hospitals throughout the country. The response from the medical officers was generous, and well over three thousand forms were filled up and returned to the Ministry. After exclusion of the cases that did not survive for more than 24 hours after admission to hospital, there remained for analysis 3,206 reports of cases treated either by chemotherapy plus serum or by chemotherapy alone. The drug most often employed was sulphapyridine, given orally and sometimes, in addition, intramuscularly or intravenously. Sulphanilamide, soluseptasine and sulphathiazole were occasionally used. The analysis gave the following results: (a) Among the total of 3,206 cases the fatality rate was 10.5%; (b) of the 3,206 cases, 849 were treated by chemotherapy plus serum with a fatality rate of 13.8%; (c) 2,357 cases were treated by chemotherapy alone with a fatality rate of 9.2%.

The meningococcus was sought in 2,993 cases and found in 91%. Examination for Group was naturally less extensive; it was successful in 489 cases, giving 90% Group I and 10% Group II. A comparison with the ascertained proportions of the Groups in former epidemic and non-epidemic times supports the opinion that an increase of Group I is a factor in epidemicity. In the cases analysed, however, Group II equalled Group I in severity of illness and excelled it in fatality.

It did not appear that the dosage of sulphonamides recommended by Banks (1939) was of importance (Banks himself considered that smaller dosage might be efficacious).

The tables given in the paper show the familiar curve of fatality, falling from infancy to adolescence and rising to old age, with the difference that in the chemotherapy class the fatality was lower in all age groups, except two, than in the chemotherapy plus serum class. At "all ages" of the total cases the fatality rate in females was higher (12.2%) than that of the males (9.3%); it may have been that owing to circumstances a larger proportion of the males received prompt treatment.

The author states that it is desirable that the value of cerebral and lumbar puncture should be defined, that is, whether or not the procedure should be reserved for diagnosis, and he asks whether the value of intramuscular injections of drugs is great enough to outweigh the risk of abscess and sloughing, and the consequent extra labour in nursing and delay in convalescence.

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SOME ASPECTS OF THE CHEMOTHERAPY OF PNEUMONIA

by T. Anderson, *British Medical Journal*, 1, 717-719, 12/6/43

The author is Physician-Superintendent of the Knightswood Fever Hospital, Glasgow, and has there had exceptional opportunities of studying the response of pneumonia to treatment. His material consists of 397 cases treated before sulphonamides were introduced, and 306 treated with sulphapyridine: these were all admitted with the diagnosis of acute primary pneumonia, and the great majority were lobar in distribution. An analysis of these cases brings out several interesting points, and justifies the author in his main conclusion that sulphonamide treatment has by no means wholly solved the problem of treating pneumonia. In the first place, infection by pneumococci of type II has been much more prevalent in Glasgow than in the south of England, and the prognosis in this type is worse. Whereas sulphapyridine has reduced the mortality in type I infections from 8% to 3%, the reduction in type II infections is from 29% to only 12%. Age is a still more important factor: in cases under 40, chemotherapy has reduced the mortality from 14% to 4%, but in those over 40 it has only fallen from 32% to 26%.

There is, as would be expected, a close correlation between bacteraemia on admission and a high fatality-rate: bacteraemia was also commonly followed by delayed resolution. Combined chemotherapy and serum treatment have not given encouraging results in the author's cases, and he leaves his reader with the impression that much remains to be done in order to improve the outlook for certain types of case. There will be general agreement with his conclusion that any report on the results of treatment in pneumonia should specify the ages of the patients, the presence or absence of bacteraemia, and the type of pneumococcus responsible.

325

THE EFFECT OF CHEMOTHERAPY ON THE MORTALITY FROM PNEUMONIA IN GLASGOW

by T. Anderson, *British Medical Journal* 2, 779-780, 18/12/43

Since the introduction of sulphonamides it has been claimed from analyses based purely on hospital records that fatality rates from pneumonia have been lowered to about $\frac{1}{3}$ of their former level. [It should be stated, however, that Martin (1942) was only able to show a reduction in the number of deaths in England and Wales in 1939-1941 as compared with 1934-1937 of possibly 12%. For Scotland the reduction was greater, perhaps 24%, but lobar pneumonia showed a greater reduction (40%) as compared with other types (16%).]

In the present paper fatality rates of notified cases of pneumonia in Glasgow are compared for the two periods 1922-1938 and 1939-1941 in age-groups. Reductions in mortality were recorded of 25% at ages under 1; 53% at ages 1 to 10; 64% at ages 11 to 20; 57% at ages 21 to 45; and 36% at ages over 45, thus showing that the improvement is least at the younger and older ages. For all ages combined, a reduction of only 30% is shown, indicating to what extent the average reduction masks the great improvement at middle life.

As notification is incomplete, and not necessarily equally so at each age-group, the method involves the assumption that the degree of incompleteness has at least been constant within each age-group throughout the total period. [Changes in the medical personnel issuing notifications over so long a period might perhaps make the validity of this assumption doubtful.]

Accepting the general view that lobar pneumonia is the more common lesion in middle life, bronchopneumonia in later life, and that it seems evident therefore that the prognosis with chemotherapy is more favourable for the former, the author discusses why this should be. He argues that in lobar pneumonia, as the organisms causing the disease are usually of a more invasive type than those associated with bronchopneumonia, individual resistance does not have to be lowered to the same extent as in bronchopneumonia to permit of infection. It is predominantly during infancy and in the age-groups 45 and over—i.e. at those periods when the impact of adverse social and economic factors have most effect—that individual resistance is most easily lowered and

to the greatest degree. For these reasons the bronchopneumonia type is more prevalent at these ages.

This suggests that chemotherapy alone is insufficient unless supported by what the author calls non-specific resistance on the part of the patient. More knowledge is required as to what means can be adopted to increase such resistance.

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¹ Martin, W. J. (1942) *Brit. med. J.* 2, 540

¹ [see BMB 74]

326

SULPHAMEZATHINE IN LOBAR PNEUMONIA: A Comparison with Sulphapyridine

by G. Melton, *Lancet*, 1, 277-278, 26/2/44

The author summarises the results of treatment of two unselected concurrent series of cases of lobar pneumonia, 134 of which were treated with sulphamezathine and 179 with sulphapyridine.

There was a mortality of 6.7% in the sulphamezathine and 11.1% in the sulphapyridine series.

The initial dose of sulphamezathine was 4 g., followed by 2 g. six-hourly. Very few toxic manifestations were seen, and a comparison of findings in the two series was in favour of sulphamezathine.

327

SULPHAGUANIDINE IN NEONATAL EPIDEMIC GASTRO-ENTERITIS

by J. L. Henderson, *British Medical Journal*, 1, 410-413, 3/4/43

In this paper from the *Simpson Memorial Maternity Hospital*, the author, who is Lecturer to the Department of Child Life and Health of Edinburgh University, records the excellent results achieved with sulphaguanidine in epidemic gastro-enteritis in the newborn, the most lethal of the commoner neonatal infections. Rice, Best, Frant & Abramson (1937) focused attention on the appalling waste of infant life in maternity hospitals in New York from this preventable alimentary infection. In the earlier literature, the paper based on the largest series of cases was published from Edinburgh (Craig, 1933). Numerous recent publications in both Britain and the U.S.A. have shown that few maternity hospitals are exempt from periodic epidemics of neonatal gastro-enteritis. The vast majority of affected infants are bottle-fed. The causal bacterium or virus still eludes identification. Six epidemics and a few sporadic cases, comprising a total of 102 infants with gastro-enteritis, occurred in the *Simpson Maternity Hospital* during the three years 1940-2. The incidence of 1.5% during this period was abnormally high.

Before the commencement, early in 1942, of sulphaguanidine therapy, the mortality rate in 72 cases was 76%. After the introduction of this drug, the mortality rate in 30 cases fell to 10%. The greatly improved results did not justify the use of controls. The mortality rate in the series of 30 cases treated with sulphaguanidine would probably have been still lower if there had not been so many very premature infants. There were 11 mature and 19 premature infants, and 8 of the premature infants weighed less than 4 pounds [1816 g.] at birth. The three fatal cases all belonged to the latter group.

The initial signs of gastro-enteritis usually appear after the first week of life. A sudden failure of appetite is the first sign of illness. Diminished vitality, a tired, sickly appearance and pallor follow within a few hours. Diarrhoea as a rule develops within a few hours of the onset, but may be delayed for 24 hours. The stools are watery in most cases. They are usually yellow and often contain mucus. The number frequently exceeds 10 a day and may be uncountable. Signs of dehydration usually appear by the second day, and rapidly become severe in the absence of appropriate treatment. The weight curve shows a sudden reversal and falls rapidly. Fever is an inconstant feature. Vomiting is a more pronounced feature in some epidemics than in others, and may be absent. Abdominal distension is common.

Treatment

(a) *General*: The following simple routine, in conjunction with sulphaguanidine therapy, has given very satisfactory

results. An initial purge has been omitted when diarrhoea has become established. Milk is entirely withheld, and 5% lactose or dextri-maltose water is given *ad lib.* every one and a half hours. If fluid amounting to 4 ounces [120 cm³] per pound [454 g.] of birth weight per day is not taken, the total must be made up to this amount by the use of the stomach-tube. Such an ample fluid intake is essential to replace the excessive loss, and to ensure adequate renal elimination. When there is much vomiting, the sugar should be given in 1/5 normal saline instead of water. In severe cases the fluid may have to be introduced by stomach-tube for several days. Only sugar and water or diluted saline should be given until the appetite returns; this may not occur before from several days to a week. The above regime, coupled with sulphaguanidine therapy, renders the parenteral administration of fluid unnecessary in most cases. The necessity for introducing milk gradually when the appetite returns must be emphasised. It is customary in the author's hospital to give it in alternate feeds in the form of either half-strength breast-milk or sweetened condensed milk diluted 12 times. The number of dilute milk feeds is slowly increased until milk is being given at every feed. Then the feeds are gradually strengthened according to the demands of the appetite.

(b) *Sulphaguanidine*: It is of the utmost importance to give full doses as early as possible. Owing to its slow absorption from the bowel and the necessity for achieving a high concentration therein, larger doses of this sulphonamide should be given than of the others. In the present series of cases the mature infants received an initial dose of 0.75 g. followed by 0.5 g. every four hours, and premature infants an initial dose of 0.5 g. followed by 0.25 g. every three hours. The latter dose is well tolerated by very premature infants provided ample fluid is given. These doses are continued for several days until there is pronounced clinical improvement with a return of appetite. It is then gradually reduced, being stopped a few days later. In some cases it was continued for as long as a fortnight. Much work remains to be done on the action of various sulphonamide compounds in neonatal gastro-enteritis and more experience with sulphaguanidine is needed.

(c) *Prophylactic*: Immediate isolation of all infants suspected of infective gastro-enteritis is essential in maternity hospitals. Confirmation of the diagnosis should be followed by strict precautions, to limit the extent and duration of the outbreak. Frant & Abramson (1938) have drawn up an excellent code of hygiene for the prevention and control of this and other infections in hospital nurseries.

Toxicity of Sulphaguanidine

Sulphaguanidine is one of the less toxic sulphonamides owing to its slow absorption from the bowel, but 20 to 25% of the drug is excreted in the urine. The maintenance of a high fluid intake is important to eliminate the possibility of excessive concentration of the drug in the urine, with crystallisation in the urinary tract. The urine of infants receiving the drug often contains a few characteristic crystals in the form of parallelogrammic plates, and needles occurring singly and in sheaves, but these should never be abundant. A recurrence of frequent defaecation, which appeared to be a delayed toxic effect of sulphaguanidine on the bowel, occurred in 8 of the 30 infants. This phase began 8 to 10 days after starting with the drug, and subsided a few days later. The stools were small in bulk and normal in appearance.

Conclusions

The author concludes that the prognosis in epidemic gastro-enteritis of the newborn has been dramatically improved by sulphaguanidine therapy. To achieve optimal results sulphaguanidine must be given in the full doses recommended. An ample fluid intake must be ensured. Fluid every 1½ hours is recommended. Tube-feeding may be necessary when there is anorexia. Parenteral administration is seldom required.

Milk should be withheld entirely until the appetite returns, and reintroduced very gradually.

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SULPHAGUANIDINE IN THE TREATMENT OF FLEXNER DYSENTERY

by H. G. Smith, *British Medical Journal*, 1, 287-288, 26/2/44

Forty-four young women of 17 to 37 (average 21) years admitted to a Scottish fever hospital with Flexner dysentery were treated with sulphaguanidine by mouth. The usual dosage was 142 g. in 10 days (in no case less than 129 g.).

In all cases the treatment resulted in non-dysenteric stools which were negative for *B. dysenteriae* (Flexner). Twenty-one of the patients developed a toxic rash, usually pink and maculo-papular and appearing on the ninth day of treatment.

In view of the high incidence of toxic rashes, the author tested for hypersensitivity by giving to 4 groups (a, b, c, d) of 3 affected patients test doses of (a) sulphanilamide (1 g.); (b) sulphathiazole (1 g.); (c) sulphadiazine (1 g.) and (d) sulphaguanidine (2 g.).

No reactions were seen in groups a, b and c. One patient in group d developed a scarlatiniform rash which faded in 20 hours. The 9 patients in groups a, b and c were subsequently each given 2 g. sulphaguanidine, and 7 of them developed toxic rashes.

Conclusions. Bacteriological results were very satisfactory, but the high incidence of toxic rashes was a serious disadvantage of the treatment. The lack of reaction to other sulphonamides in the sensitive subjects suggests that the guanidine radical may be the sensitizing agent. The author comments that children tolerate high doses of sulphaguanidine without adverse effects.

329

STAPHYLOCOCCAL SEPTICÆMIA TREATED WITH SULPHADIAZINE

by H. B. Norman, *British Medical Journal*, 1, 183, 5/2/44

A case of staphylococcal septicæmia is reported in which a dramatic response was obtained with sulphadiazine after sulphathiazole had proved ineffective. The patient, a soldier aged 32, was admitted to hospital complaining of aching in the limbs and malaise for one week. A fortnight earlier he had had a boil on the back of his neck. On admission, temperature was 101° F. [about 38.3° C.] and the blood count showed: hæmoglobin 84%, erythrocytes 4,690,000 per mm.³, colour index 0.91, leucocytes 14,000. The patient was given full doses of sulphathiazole. A week later *Staph. aureus* was cultured from pus obtained from a fluctuant nodule on the left arm. The patient's condition continued to deteriorate and 18 days after admission sulphathiazole was stopped, after a total administration of 60 g. without obvious benefit. The administration of sulphadiazine was begun and a total of 100 g. was given over 12 days. The response was immediate and within 8 days the patient's condition was satisfactory. Later, in view of the prolonged septic infection and moderate anaemia, 1 pint of blood was transfused intravenously; hæmoglobin was 96% after transfusion. Convalescence thereafter was uneventful.

330

THE RÔLE OF CHEMOTHERAPY IN THE TREATMENT OF HÆMATOGENOUS OSTEOMYELITIS

by K. C. McKeown, *British Journal of Surgery*, 31, 13-22, July 1943

A series of 26 cases of acute hæmatogenous osteomyelitis was treated with sulphathiazole and various types of surgical intervention. Details of variations in the treatment of all cases are given and there are 12 radiographs.

In the 17 cases which received early sulphathiazole combined with bone drilling, the degree of bone change shown in the radiographs was minimal. In 2 of these cases there were no radiographic changes, although the diagnosis was not in doubt. The dosage of sulphathiazole was 1 g. per 20 lb. [about 9 kg.] body weight per day for 8 days, beginning at the onset of the disease. After an interval of 3 weeks the course was repeated. Usually the surgical treatment consisted in making multiple holes in the metaphysis between the second and sixth days of the disease.

In the remaining cases in which surgical intervention was minimal (3 cases) or different (2 cases), or in which sulphathiazole was administered later (3 cases) or in smaller dosage (1 case), the severity of bone infection did not appear to be

modified by chemotherapy. Results were compared with a control series of 74 cases treated without chemotherapy.

The duration of the disease appeared to be considerably shortened in those cases in which sulphathiazole was employed, although the data were incomplete in some respects. Combination of sulphathiazole and bone drilling appeared to reduce the duration of the disease by 60 %.

331

SULPHANILAMIDE IN THE TREATMENT OF SMALL-POX

by P. B. Wilkinson, *Lancet*, 2, 67-69, 18/7/42

Working in Hong Kong during the smallpox epidemic which raged from November 1937 to July 1938, the author was able to study the effect of sulphanilamide in this disease. The epidemic was characterised by the occurrence of a high percentage of toxic or hæmorrhagic cases, and therefore afforded an admirable opportunity of testing the effect of the drug in all types of smallpox. In a preliminary discussion the author notes the following points. Smallpox is a diphasic disease, the two phases being the toxic and the focal. The focal phase is merely a sequela of the toxic phase, and is not to be regarded as an essential part of smallpox proper. It is necessary to know the vaccinal history of the patient before attempting to assess the use of any drug in the treatment of either phase of smallpox, because vaccination profoundly modifies the character of the toxic phase as well as the number and type of lesions seen in the focal phase.

The effect of sulphanilamide on both phases of the disease was observed in a series of 103 patients. The drug was given in powder form by mouth in a dose of 1 g. four-hourly, with necessary modifications for age. No initial loading dose was employed.

The results were as follows: of the 13 toxic or hæmorrhagic cases treated with the drug not one recovered, and in no case was there any sign that the toxic phase of the disease was in the least modified. The remaining 90 patients in the series were divisible into two groups: 41 who had been previously vaccinated, and 49 who had not. In only 19 of the 49 unvaccinated patients was the evolution of the focal lesions obviously changed, the change most commonly seen being an arrest of the lesion at the vesicular stage. In other words, the lesions dried up instead of becoming mature pustules, leaving the face and body covered with a multitude of small horny pocks. These 19 patients showed no secondary focal or septic fever. The other 30 unvaccinated patients showed no modification of the natural course of the disease as a result of sulphanilamide therapy.

In the second group of 41 vaccinated patients, the drug was used because of some septic complication which had arisen during the course of the disease. The most frequently observed complications were boils, muscle abscesses, skin sloughing, cellulitis, otitis media and furunculosis of the external auditory meatus; rarer complications were panophthalmitis, suppurative arthritis, suppurative periostitis and streptococcal infections of the genito-urinary tract. Results in these cases were dramatic, and once adequate drainage had been established, recovery tended to be prompt and uninterrupted provided an adequate dosage of sulphanilamide was employed.

The figures for the three groups in the series of 103 patients are as follows:

	Toxic	Focal Phase	
		Unvaccinated	Vaccinated
Cases treated	13	49	41
Deaths	13	11	2
Fatality rate	100 %	22.4 %	4.8 %

As a result of these observations the author concludes: (i) that the toxic phase of smallpox is unaffected by sulphanilamide; (ii) that the focal phase is modified in a certain number of unvaccinated patients in the sense that the normal evolution of the lesions is arrested at the vesicular stage; (iii) that the septic complications which so often occur in the focal phase are profoundly influenced by the drug, which is indeed life-saving in some of these cases. He therefore advocates the use of sulphanilamide in the focal phase because this measure reduces the fatality rate in those cases showing septic complications, and helps to abort the focal phase in a certain percentage of cases.

Arsenical and Antimonial Compounds*

332

THE STANDARDISATION OF THE THERAPEUTIC POTENCY OF NEOARSPHENAMINE AND SULPH-ARSPHENAMINE

by F. Hawking, *Quarterly Journal of Pharmacy & Pharmacology*, 16, 13-24, January & March 1943

The author, from the Department of Biological Standards of the Medical Research Council, describes the reorganisation of the tests used in the biological standardisation of neoarsphenamine, and the statistical principles on which the framing of such tests depends. Two groups each of 10 mice suitably infected with *T. equiperdum* are taken. The mice of the first group are given intravenously a dose (x) of the sample of neoarsphenamine under test, dissolved to form a 0.1 % solution. The mice of the second group are similarly treated with the standard preparation, the dose of the standard ($0.8x$) being 80 % that of the sample under test. The dose of the standard is chosen so as to give approximately a 50 % response. The blood of the mice is examined microscopically on the first and third days after the treatment, and if no trypanosomes can be found on the third day the corresponding mouse is regarded as "cured." If the sample under test "cures" two (or more) mice more than the standard "cures," it is accepted without further trial. When it fails to do this, the test is repeated once; if the total number of mice "cured" by the sample is equal to or greater than the number "cured" by the standard, the sample is passed for commercial sale; if not, it is rejected.

This arrangement of the doses allows for the passing of samples with a therapeutic potency 20 % less than that of the standard preparation, as recommended by the International Conference. By statistical analysis, based on the logarithm-dose: probit-response curve, it is shown that only 1.7 % of batches of neoarsphenamine having a potency 9 % less than the regulation level (80 % of that of the standard preparation) would be incorrectly passed on the first test, and only 1.7 % of batches having a potency 10 % above the regulation level would be incorrectly rejected. The accuracy is consequently high. The test has proved convenient and simple to carry out, and the principles on which it is based will be applied to other tests when the opportunity comes.

333

TREATMENT OF LYMPHOGRANULOMA INGUINALE WITH ANTHIOMALINE

by W. A. Law, *Lancet*, 1, 300-304, 6/3/43

[Lymphogranuloma inguinale has attracted increased interest since it became recognised as a venereal disease caused by a virus, and widespread in temperate as well as tropical parts of the world. The tendency of most uncomplicated cases to heal spontaneously after some weeks or months makes it difficult to estimate the value of a method of treatment. Various remedies that have been tried include the therapeutic use of Frei antigen, protein shock therapy with T.A.B. vaccine or "Pyriker" (a preparation of *B. coli*), gold salts, various compounds of antimony, and sulphonamides. "Anthiomaline," a compound (lithium antimony thiomalate) containing 16 % of antimony, was used with apparent success in Paris in 1935 by Sezary, and Shaffer (1942) considered it to be as effective as the sulphonamides, sometimes acting when the latter failed and *vice versa*.]

The present paper is a detailed study of the disease by a surgical specialist in the British army in West Africa. During eighteen months he treated 220 cases, of whom 33 were European and 187 Africans, all previously fit soldiers. All except three, in whom the neck glands were infected, were genital and inguinal cases, and there was no rectal involvement. Over 85 % of the Africans were circumcised, this being usual among them, and the author suggests that their infection, as with syphilis, was probably due to some minor abrasion during coitus.

Diagnosis. In nearly all cases the clinical diagnosis was confirmed by Frei's intradermal test, the Kahn test, the use of a Dmelcos vaccine test, microscopical examination for

* [see also BMB 303, 314 & 337]

spirochaetes and gonococci, and biopsy with histological section. The Frei test was positive in 61 %, doubtfully positive in 16 %, and negative in 15 %, and in the remainder (17 cases) it was not done owing to lack of antigen. It was not possible to make other tests except the "vesicular test" of Ottolina (1941) which was tried in 20 cases of which 10 were strongly Frei-positive; only one positive vesicular reaction was obtained and that was in a previously Frei-negative patient. The author found the small nodule called "Fischer's Knötchen," which develops in Frei's test, very useful for diagnosis in African patients.

Primary lesion. This was observed in 52 cases; an intra-urethral papule mentioned by Romanis & Mitchiner (1941) was not encountered although it was searched for.

Bubo. The author describes the "bubo" clinically and pathologically in the four progressive stages suggested by Stammers & Law (1941), each of which readily merges into the succeeding stage. Histological section showed infiltration of the tissues by mononuclear cells and multiple areas of focal necrosis. There were few polymorphonuclear cells.

Treatment. The author emphasises the need to prevent secondary infection and condemns incision and drainage or scraping and packing with gauze. In the relatively few early cases, excision of the gland was effective and healing occurred within 2 or 3 weeks. When softening had taken place aspiration was performed, taking care to seal the puncture hole afterwards. As the disease is not merely a local lesion, the author changed from purely surgical measures to the use of anthiomaline, given intramuscularly in cases seen earlier, and intravenously in the later cases of the series. The injections were given two or three times a week beginning with 0.5 cm.³ and increasing by 0.5 cm.³ up to 2 cm.³ with a maximum of twenty injections and a total dose of 0.2 g. When anthiomaline was not available a 1 % aqueous solution of sodium antimony tartrate was substituted, beginning with 1.5 cm.³ and increasing by 1.5 cm.³ up to 6 cm.³ given twice a week. Relief of pain was often dramatic after two or three injections. No ill effects were seen, except a mild pyrexia a few hours after an intravenous injection.

The patients were not kept in bed and were able to do light work in hospital; three Europeans in the fourth stage [see above] with fistula and ulceration were treated successfully while carrying out their normal duties.

The average number of injections required was ten, during a little over three weeks. To avoid relapse it was found advisable to give eight or more injections, even if the glandular swelling had subsided before the completion of the course.

In one African in the second stage, a coherent mass of glands with a central cavity containing sterile pus was removed from the right groin. The wound healed promptly, but the scar became keloid. The glands of the left side were left, and anthiomaline was given intravenously. The glandular swelling subsided without any complication within the time required (8 days) for the healing of the right side.

Sulphanilamide. Forty-five cases were treated with sulphanilamide, which was given orally as tablets—2 g. every 4 hours for 48 hours, then 1 g. every 4 hours for 72 hours, then 1 g. every 8 hours for 48 hours; after an interval of 5 to 7 days this course was repeated. The results were satisfactory but rather less so than with antimony, and the patients required to be kept in bed for the whole period. Blood leucocyte counts were made at intervals during this treatment.

Relapses. Twelve cases relapsed and the Frei test remained positive. The glandular swelling recurred in 4 to 12 weeks after subsidence of all symptoms and signs, and in all cases another course of anthiomaline produced a satisfactory result.

The author concludes that the results with anthiomaline compared favourably with those from other methods, including sulphanilamide.

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Some New Synthetic Drugs

334

PHEMERIDE: A NEW ANTISEPTIC DETERGENT

by C. N. Iland, *Lancet*, **1**, 49-51, 8/1/44

Tests were made on a new organic detergent, phemeride or phemerol (*para*-tertiary-octyl-phenyl-diethoxy-benzyl-dimethyl ammonium chloride). It is a quaternary ammonium compound and contains a long aliphatic chain; it resembles cetavlon, the new detergent which was first described as CTAB (cetyl-trimethyl-ammonium bromide). According to the classification of Baker, Harrison & Miller (1941) it is a cationic detergent and therefore more active against gram-positive than gram-negative organisms, and more germicidal to either than the anionic detergents. The germicidal action of these substances is probably due to disruption of or interference with the functions of the bacterial cell-membrane. *In vitro* tests showed phemeride to inhibit the growth of *Staph. aureus* in a dilution of 1:400,000; *Strept. pyogenes*, *C. diphtheriae* and *Cl. welchii* were inhibited with a dilution of 1:200,000. Gram-negative organisms were less sensitive; *E. coli* was inhibited with a dilution of 1:160,000, *P. vulgaris* with 1:4,000 and *Ps. pyocyanea* with 1:2,000.

Phemeride has a relatively low toxicity to leucocytes. A dilution of 1:4,000 stopped phagocytosis in 4 hours; 1:8,000 did not stop it after 5 hours. The anti-bacterial action of phemeride does not appear to be closely related to the size of the inoculum.

A small series of clinical tests was made. Phemeride was found to be an efficient skin antiseptic; no sign of skin sensitivity developed from its use. In a few observations made on infected thoracic wounds and fistulae there appeared to be a diminution of infection in some cases, but results were not conclusive. No toxic symptoms were seen. The authors conclude that phemeride has good bactericidal properties and is relatively non-toxic to the tissues. It can be placed in open wounds and the pleural cavity without apparent damage.

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335

THE LETHAL ACTION OF BENZYL BENZOATE, DIMETHYLTHIANTHRENE ("MITIGAL") AND TETRAETHYLTHIURAM MONOSULPHIDE ("TETMOS") ON THE SCABIES-PRODUCING MITES, *NOTOEDRES* SP. AND *SARCOPTES SCABIEI* VAR. *HOMINIS*, WHEN TESTED *IN VITRO*

by R. M. Gordon & K. Unsworth, *Annals of Tropical Medicine and Parasitology*, **37**, 195-199, December 1943

Benzyl benzoate, dimethylthianthrene (mitigal), and tetraethylthiuram monosulphide (tetmos) are all known to be effective sarcopticides in the treatment of scabies. The authors describe experiments with *Notoedres* (from infected rats) and the human scabies parasite (*Sarcoptes scabiei* var. *hominis*) on the relative efficiency *in vitro* of these three compounds, all of which were used in 5 % solution. Earlier tests with 10 % solutions were discontinued because the parasites perished too quickly to permit comparative observations.

After immersion in 5 % tetmos for 10 hours, only 6 % of the *Notoedres* survived. With mitigal and benzyl benzoate the corresponding percentage survival was 59 and 90.

Similar experiments were performed with the human parasite. Fewer of these were available, and comparison was made only between tetmos and benzyl benzoate. Resistance to both compounds was greater than in the case of *Notoedres* but tetmos was clearly more effective.

The authors emphasize that the results of *in vitro* tests may not have a direct clinical application. For example, it is well known that the human scabies parasite will survive for days in sulphur ointment. The efficacy of sulphur ointment in the treatment of scabies is presumably due to the liberation of active products produced after application to the body.

[An account of the clinical use of tetmos (described as T.E.T.M.S.) will be found in *BMB* 78.]

TUBERCULOSIS TREATED WITH PROMIN

by F. R. G. Heaf, J. V. Hurford, A. Eiser & L. M. Franklin, *Lancet*, 1, 702-704, 5/6/43

The use of "promin" (sodium p:p'-diamino diphenyl sulphone-N:N'-didextrose sulphonate) in the treatment of pulmonary tuberculosis is still in the experimental stage. This article is an interim report on work which is continuing, and consists of the findings in 18 cases of pulmonary tuberculosis (4 with tuberculosis of the larynx as well) and 1 genito-urinary case.

Methods and dosage. The drug was given in courses averaging 8½ weeks, and in this period the administration was continuous for 2 weeks and was followed by a week's rest. Total dosage varied from 8.4 g. to 96.8 g., and exceeded 30 g. in 10 cases. The oral route was used in 13 cases and the intravenous in 2 (including the genito-urinary case).

A period of bed-rest averaging 23 weeks preceded the promin treatment in the pulmonary cases, and acted as a control. During this period the cases were largely stationary. The clinical state was assessed by x-rays, hæmograms, temperature, weight, and sputum examination. The promin content in blood and urine was estimated weekly. Examinations of blood and urine for abnormal pigments, and blood counts and hæmoglobin estimations were done regularly.

Laboratory investigations. The level of promin in the blood did not follow the dosage at all closely. 2.5 mg. per 100 cm.³ was the average blood concentration with oral administration. The hæmoglobin fell in all cases until iron was given as a routine. In only one case was the leucocyte count affected. The promin concentration in the urine was high (sometimes more than 100 mg./100 cm.³), and well maintained during the rest periods. With the intravenous dosage the blood concentration averaged 1 mg. per 100 cm.³ during administration, and 0.7 mg. during the rest period.

Clinical results. The 14 purely pulmonary cases comprised 8 cases of fibro-caseous disease with excavation, 1 pneumonic case, 3 cases of limited disease of the exudative type, and 2 thoracoplasty cases with spread to the other side. There were no adverse symptoms from the intravenous dosage. The oral cases had cyanosis, headache, nausea, and giddiness, all of moderate degree. Results are seen in the following table:

Clinical State	Cases	Worse or dead	No change	Slight improvement	Definite improvement
Advanced, poor resistance	2	2	0	0	0
Advanced, good resistance	5	0	2	1	2
Moderate disease	4	0	2	0	2
Limited disease	3	0	2	0	1

The genito-urinary case improved considerably. It was thought that promin probably had a deleterious effect on one patient who died, an advanced case with poor resistance.

Laryngeal application. Four cases were treated, 2 with insufflation of a powder containing promin, and 2 by painting the larynx with a 50% promin in glycerine paint. The latter 2 cases improved.

Conclusions. Results were indefinite, but the authors' impressions of the value of promin were, in general, negative. The following conclusions appear to them to be justifiable: (i) Oral promin produces moderately unpleasant toxic symptoms and hæmolytic anæmia, (ii) the anæmia is prevented by iron, (iii) the intravenous route produces no toxic symptoms nor anæmia, (iv) promin is not suitable for advanced cases with poor resistance, (v) the local application of promin in laryngeal tuberculosis is worthy of further investigation.

Routes of Administration: Local Reactions

337

STUDIES IN CHEMOTHERAPY. XXXIV—COMPARISON OF THE RESULTS OBTAINED BY DIFFERENT METHODS OF ADMINISTRATION OF DRUGS IN TRYPANOSOMAL INFECTIONS IN MICE

by J. D. Fulton & W. Yorke, *Annals of Tropical Medicine and Parasitology*, 37, 80-95, September 1943

Whatever route or systemic administration may be adopted, its efficacy depends upon attaining a certain concentration of drug in the blood-stream. Preliminary trials of new compounds for trypanocidal or spirochætocidal action are almost invariably performed in mice, but routes of administration vary. No systematic investigation of the best route for this purpose seems to have been reported, and the authors have accordingly undertaken an investigation of the results of treatment of large numbers of mice by oral, subcutaneous, intraperitoneal and intravenous administration of 6 drugs (tryparsamide, tryparsamide thioglycollate, neoarsphenamine, diamidino monomethyl stilbene, diamidino dimethyl stilbene, 7 amino-9 (p-aminophenyl)-10 methyl phenanthridinium chloride).

It was found that the best therapeutic indices

$$\left(\frac{\text{maximum tolerated dose}}{\text{minimum effective dose}} \text{ and } \frac{\text{maximum tolerated dose}}{\text{minimum curative dose}} \right)$$

were obtained by subcutaneous administration, although in the case of tryparsamide and reduced (trivalent) tryparsamide some other routes gave as good results. All the compounds tested, except tryparsamide, caused bald patches or ulcers at the site of injection.

Points for and against other routes of administration are discussed and the experimental results are tabulated.

A comparison of the relative efficacy of the drugs used showed that the highest therapeutic index in the treatment of *T. rhodesiense* infections was obtained by subcutaneous diamidino monomethyl stilbene. In the case of *T. congolense* infections the value $\frac{\text{maximum tolerated dose}}{\text{minimum effective dose}}$ was highest for the phenanthridinium compound subcutaneously. The highest $\frac{\text{maximum tolerated dose}}{\text{minimum curative dose}}$ ratio was shared by subcutaneous phenanthridinium compound and subcutaneous diamidino dimethyl stilbene.

338

ADMINISTRATION OF NON-STEROID SUBSTANCES BY THE IMPLANTATION TECHNIQUE

by A. S. Parkes, *Journal of Endocrinology*, 3, 220-233, August 1942

The technique of administration of steroid hormones by implantation of compressed tablets of pure crystalline material was first devised by Deanesly & Parkes (1937). Complete absorption is slow, since steroid substances have a low solubility in body fluids. The present paper from the *National Institute for Medical Research* reports attempts to adapt the implantation technique to substances such as adrenaline, insulin and gonadotrophins which are easily soluble in body fluids and to thyroxine which is very poorly soluble. As compressed tablets of highly water-soluble substances were rapidly dissolved, a search had to be made for a suitable excipient. The following substances were rejected: stearic acid, palmitic acid, uric acid, starch, kaolin, lumisterol, ergosterol and sitosterol. Observations made in another investigation had suggested that sulphonamide derivatives might be useful excipients, and it was found that sulphanilamide was absorbed very rapidly, sulphapyridine and sulphathiazole more slowly, and benzyl sulphanilamide very slowly. Cholesterol was the other excipient found most useful for delaying the absorption of water-soluble substances, although its mode of action is not obvious.

In tests carried out with the highly water-soluble substance dextrose by implantation into rats and rabbits, complete absorption was delayed for weeks by incorporating the dextrose in 100 mg. tablets containing 90% cholesterol. Pure dextrose is absorbed within a few hours after transplantation.

Benzyl sulphanilamide was found to have little effect in retarding the absorption of dextrose. Adrenaline in high concentration was usually fatal, but tablets containing 15% adrenaline and 85% cholesterol lost between one-quarter and one-third of their adrenaline in 28 days.

It has been shown (Parkes & Young, 1939) that insulin is absorbed almost as quickly by implantation in tablet form as by subcutaneous injection in solution. In the present paper no observations are reported on metabolism after implantation of insulin, except as to whether the treatment was lethal. Low-zinc insulin and crystalline insulin in concentrations of 5 to 25% in 100 mg. tablets with cholesterol as excipient were usually fatal. Female rats were less sensitive than male rats. Only some 2-3 mg. of insulin were absorbed in the course of a month in animals which survived. The author concludes that the implantation technique is more effective than a simple injection in the case of crystalline insulin.

Chorionic gonadotrophin (10%) was absorbed rapidly from 100 mg. tablets with cholesterol as excipient. Much had been absorbed within 1 day and all within 6 days. Pituitary gonadotrophins were similarly absorbed rapidly. Experiments with a sheep pituitary extract, however, showed that the effectiveness of the extract was greatly increased when it was absorbed from a tablet, as against the increase in ovarian weight produced by daily subcutaneous injection. Thyroxine was not absorbed in weighable amounts from tablets implanted for many months, and no satisfactory excipient has yet been found to expedite absorption. The author considers that the implantation technique might be convenient when chronic administration of substances such as adrenaline is required.

REFERENCES

- Deanesly, R. & Parkes, A. S. (1937) *Proc. roy. Soc. B.* **124**, 279
Parkes, A. S. & Young, F. G. (1939) *J. Endocrinol.* **1**, 108

339

DEPOSITION OF PROTEIN MATERIAL IN IMPLANTED PELLETS OF STEROID HORMONES

by R. Deanesly & A. S. Parkes, *Lancet*, **2**, 500-502, 23/10/43

Folley (1942a) described an interstitial deposit of protein matter in tablets of diethylstilbæstrol which had been implanted subcutaneously into heifers. He suggested (1942b) that this interstitial deposit would progressively retard absorption of the implant. Shimkin & White (1941) introduced fused blocks of compounds for implantation. These blocks, in contrast to compressed tablets, have no interstices and should therefore offer less opportunity for deposition of protein matter.

The authors report experiments at the *National Institute for Medical Research* in which a comparison was made of the fate of compressed tablets and fused blocks of œstradiol, testosterone, progesterone, and desoxycorticosterone acetate. All tablets and blocks were of approximately the same weight (50 mg.) and shape, and they were implanted in rats.

There was a deposition of protein both in tablets and fused blocks, although, in the latter, the protein body left behind after ether extraction was thin-walled and apparently hollow, whereas in the case of the tablets the deposit extended throughout its substance.

Histological examination revealed no evidence of the inclusion of living tissue in the protein meshwork, nor did there appear to be any histological connection between the protein deposit and the connective-tissue capsule which surrounded the implant. There was no evidence that the interstitial protein deposit retarded absorption of the implanted material.

REFERENCES

- Folley, S. J. (1942a) *Nature*, **150**, 403
Folley, S. J. (1942b) *Nature*, **150**, 735
Shimkin, M. B. & White, J. (1941) *Endocrinology*, **29**, 1020

340

ACRIDINE ANTISEPTICS: Further Experiments on their Local Action

by D. S. Russell & M. A. Falconer, *Lancet*, **1**, 580-581, 8/5/43

The antiseptic action of the acridine compounds was first discovered by Browning and his colleagues who introduced

acriflavine for use in wounds during the 1914-18 war. This compound enjoyed wide popularity at first because it acted in the presence of serum and was apparently not toxic to leucocytes; but later work showed that the concentrations used in wounds were less innocuous than was first supposed. Moreover, much of the solution applied to wounds was removed by fixation on the gauze dressings. For these and other reasons its use became restricted. Interest in the acridine series was revived at the beginning of the present war, and Russell & Falconer (1940) showed that proflavine (2:8-diamino-acridine) was less harmful to the tissues than acriflavine; as an 0.1% solution in isotonic saline buffered to pH 6.2 it could be applied to the exposed surface of the cerebrum of rabbits without causing any appreciable damage. The same authors have now shown in the present paper that similar solutions of two other derivatives—5-mono-amino-acridine hydrochloride and 2:7-diamino-acridine mono-hydrochloride—may be employed in a similar manner without harm to the cerebrum. Their technique involved the removal of a triangular area of the skull about 2×1.5 cm. over the cerebrum and the application for 10 minutes of a pledget of "lintine" soaked in the acridine solution, after reflection of the dura and scarification of the exposed leptomeninges in three or four places. At the same time 0.1 cm.³ of the solution was injected into the cerebral cortex. The animals were killed after 1, 2, 4 and 8 days respectively, and the brain was examined by the usual histological methods. After this procedure the brain appeared macroscopically normal apart from trivial hæmorrhages. Microscopically, there were slight hæmorrhages and infiltration of polymorphonuclear leucocytes in the leptomeninges, and the neurones of the superficial cortical tissue were frequently shrunken and hyperchromatic. Fibroblastic proliferation was in progress by the 4th day and was conspicuous by the 8th day. But altogether the lesions were limited in extent and they were not much greater than those caused by isotonic saline applied in the same manner. Other members of the acridine series such as acriflavine and euflavine, however, were highly toxic and damaging. From these experiments Russell & Falconer conclude that solutions (0.1%) of proflavine sulphate, 2:7-diamino-acridine, and 5-amino-acridine hydrochloride, made up in isotonic saline and buffered to pH 6.2 are suitable for the prophylactic treatment of wounds, since the damage which they may cause is small compared with the benefit of avoiding bacterial infection.

Another method of using proflavine has recently been described by Mitchell & Buttle (1942) working in Egypt. They were dealing with suppurating wounds, first seen about 5 to 12 days after infliction: most of the wounds were heavily infected, and some had resisted other forms of treatment. These workers cleaned the wounds surgically and then inserted proflavine sulphate, as powder, in quantities from 0.5 to 2.0 g. In all but 6 of their 80 cases great improvement followed this treatment. The present authors have now imitated this method experimentally by applying 0.02-0.05 g. of the powder to the brains of rabbits as described above. Proflavine, 2:7-diamino-acridine, and 5-amino-acridine were tested. In all cases complete necrosis of the underlying brain was caused, with œdema and hæmorrhage of the more distal portions. Similar results were obtained by Hawking (1943), who inserted 10 mg. of various acridine derivatives as powder into subcutaneous wounds of rats; in all cases widespread necrosis was caused. It is concluded that although proflavine powder may have a beneficial effect when applied to chronic suppurating wounds, it should *not* be applied prophylactically to fresh wounds, since it causes so much damage.

REFERENCES

- ¹ Russell, D. S. & Falconer, M. A. (1940) *Lancet*, **2**, 100
² Mitchell, G. A. G. & Buttle, G. A. H. (1942) *Lancet*, **2**, 416
³ Hawking, F. (1943) *Lancet*, **1**, 710
¹ [typescript abstract available on request]
² [see BMB 57] ³ [see BMB 341]

341

HISTOLOGICAL EFFECT OF PROFLAVINE POWDER ON FRESH WOUNDS

by F. Hawking, *Lancet*, **1**, 710-711, 5/6/43

In this short paper from the *National Institute for Medical Research*, London, the author shows that the application

of powdered proflavine sulphate to experimental wounds in subcutaneous tissue is followed by necrosis. Rats were used as test animals, and 10 mg. of the powder was inserted into pockets formed by lifting up the 3-4 cm.² of skin around the incision, which was then loosely sutured. The rats were killed at intervals of 2-20 days after operation and the site was examined histologically. Proflavine hydrochloride, proflavine salicylate, proflavine *p*-hydroxy phenyl sulphonate, proflavine hydroiodide, neutral proflavine sulphate, proflavine base, and 5-aminoacridine hydrochloride were tested and 14 untreated wounds were observed as controls.

Control wounds healed completely in 10 days. Treated wounds showed great effusion of fluid in the connective tissue planes, and necrosis of skin, subcutaneous tissue, and underlying muscle. No convincing variation in toxicity of the different compounds was seen.

The author concludes that acridine antiseptics should not be applied in powder form to fresh wounds. This conclusion does not affect the use of such powders in chronic suppurating wounds, as reported by Mitchell & Buttle (1942).

REFERENCE

- ¹ Mitchell, G. A. G. & Buttle, G. A. H. (1942) *Lancet*, 2, 416
¹ [see BMB 57]

342

HISTOLOGICAL EFFECTS OF SULPHONAMIDE-PROFLAVINE MIXTURES IN THE RABBIT: Some Experimental Observations

by D. S. Russell & D. J. K. Beck, *British Medical Journal*, 1, 112-113, 22/1/44

It has been shown (Russell & Falconer, 1943; Hawking, 1943) that acridine powders have a highly destructive effect upon the tissues. The present paper, from the *Nuffield Department of Surgery*, Oxford, reports the histological effects of the local application of proflavine powder diluted with sulphathiazole powder. About 0.25 g. of a powder composed of 1 part of proflavine sulphate to 99 parts of sulphathiazole was inserted in the wounds made in the leg muscles of rabbits. In the opposite legs sulphathiazole alone was inserted. The animals were killed at different intervals after the operation and the tissues were examined. Macroscopically, the surrounding tissues of wounds containing pure sulphathiazole showed slight oedema with traces of hæmorrhage, but the mixed powder caused severe oedema, discolouration and petechial hæmorrhages. Microscopically, the changes caused by sulphathiazole alone were not significant, but in wounds into which the mixed powder had been inserted there was persistent local oedema with hæmor-

rhagic necrosis in the dermis, the panniculus carnosus, and the subjacent muscle and its fascia.

In similar experiments on the central nervous system, sulphapyridine was used instead of sulphathiazole because of the known epileptogenic properties of the latter (Watt & Alexander, 1942). In a few animals sulphadiazine was used. Craniotomy was performed on 28 rabbits and proflavine and sulphonamide powder in varying proportions was applied. There was a lack of uniformity, which the authors find difficult to explain, in the histological reactions. It was clear, however, that the severity of the reaction was proportional to the concentration of proflavine in the mixture.

These results confirmed previous reports on the harmlessness of sulphathiazole powder to the tissues. Considerable damage to muscle and connective tissue is caused by the addition of 1 % proflavine sulphate to the powder. Experiments on the rabbit's brain indicate a similar damaging effect of proflavine on nerve tissue, although results are not so conclusive.

REFERENCES

- ¹ Hawking, F. (1943) *Lancet*, 1, 710
² Russell, D. S. & Falconer, M. A. (1943) *Lancet*, 1, 580
³ Watt, A. C. & Alexander, G. L. (1942) *Lancet*, 1, 493
¹ [see BMB 341] ² [see BMB 340] ³ [see BMB 55]

343

INTRAMUSCULAR INJECTION OF MEPACRINE (ATEBRIN): Histological Effect

by F. Hawking, *British Medical Journal*, 2, 198-199, 14/8/43

Previous writers have stated that intramuscularly injected mepacrine (atebrin) causes no local reaction in most cases, pain and swelling in some, and occasionally local abscesses. No histological observations on this subject appear to have been published previously. The experiments reported in the present paper from the *National Institute for Medical Research* were made on rabbits weighing 1.5 to 2 kg. Mepacrine methanesulphonate (atebrin musonate), 50 mg. in 0.5 cm.³ distilled water, was injected intramuscularly and subcutaneously, and the animals were killed at varying intervals for histological examination. Some experiments were also made in rats.

Macroscopic evidence of injury was usually slight, but microscopical examination always showed some necrosis at the site of injection. Similar experiments were made with quinine monohydrochloride. The damage caused by mepacrine was similar to, but rather less than, that following quinine. It was not so extensive as to be a contra-indication to parenteral administration, but sufficient to indicate that this route should not be chosen without due consideration.

344

BOOKS, MEMORANDA, REPORTS

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344/9

THE MEDICAL USE OF SULPHONAMIDES

Medical Research Council War Memorandum No. 10.
London, H.M. Stationery Office, 1943. 46 pages. 9d. [£0.04]

This authoritative and exceptionally useful Memorandum was prepared for the Therapeutic Requirements Committee of the *Medical Research Council*. It is hardly an exaggeration to say that it contains all that is necessary for the physician or surgeon to know about the sulphonamides.

In the chapter on Chemistry the synonyms, structural formulæ, chemical descriptions, and essential physical properties of nine principal sulphonamide drugs are given. The section on Pharmacology deals with the mechanism of sulphonamide bacteriostasis, the development of sulphonamide-resistance, and the conditions of absorption and excretion by the body. In the next section the principles of optimal dosage are expounded, and the differences in dosage schemes for (i) acute, (ii) sub-acute and chronic, and

(iii) urinary infections, are indicated. There is a useful table of dosages for (a) severe and (b) moderate infections at different ages. Examples are given of dosages employed in sulphonamide prophylaxis. There are brief sections on the various routes of administration and on the regulation of dosage by determination of the sulphonamide content of the blood. There follows a long section in which the treatment of specific infections is discussed in some detail as follows: (i) Hæmolytic streptococcal infections; (ii) Non-hæmolytic streptococcal infections; (iii) Meningococcal infections; (iv) Other forms of purulent meningitis; (v) Pneumonia; (vi) Staphylococcal infections; (vii) Peritonitis; (viii) Urinary tract infections; (ix) Venereal diseases; (x) Wounds; (xi) Gas gangrene; (xii) Burns; (xiii) Intestinal infections. There are short notes on sixteen other diseases, in most of which sulphonamide treatment does not rest on as sound a foundation.

The last section is devoted to a very adequate discussion of toxic reactions to sulphonamides. This includes a table of toxic effects of sulphanilamide, sulphapyridine, sulphathiazole and sulphadiazine, which has been adapted from Circular Letter No. 17, issued by the Surgeon General, Washington.

There are two Appendices. The first summarises the Bratton & Marshall and the *p*-dimethylaminobenzaldehyde methods for the determination of sulphonamide-concentration in body fluids, while the second is devoted to recent recommendations on the sterilisation of sulphanilamide powder.

344/10

PATHOLOGICAL HISTOLOGY

by R. F. Ogilvie. 2nd edition. Edinburgh, E. & S. Livingstone, 1943. 411 pages ; 235 coloured plates. £1 12s. 6d. [£1.625]

This book is intended as a companion to larger textbooks and for use in practical pathology. Its principal feature is the series of beautifully reproduced photomicrographs in colour. New matter and more coloured plates have been added to the new edition ; many sections of the existing text have been revised. There are few conditions met with in the practical histology class which are not represented in the book. The first edition was by some authorities considered the most outstanding textbook of morbid anatomy in the English language.

344/11

DISEASES OF INFANCY AND CHILDHOOD

by W. Sheldon. 4th edition. London, J. & A. Churchill, 1943. 748 pages ; 144 illustrations. £1 8s. [£1.4]

This book has become a standard text on pædiatrics, and the new edition shows evidence of careful revision. Advances in general medicine applicable to diseases of children are incorporated. This applies particularly to the sections on prematurity and diseases of the newborn. War-time measures regarding milk, vitamins, etc. are dealt with, and there are appendices on the sulphonamides and on the proprietary forms of vitamins at present available. In conformity with their usual standards, the publishers have, despite war-time difficulties, produced a book of the highest quality, equipped with good illustrations and index. It should be of value both to the clinical student and the general practitioner.

344/12

DISEASES OF THE NERVOUS SYSTEM

by F. M. R. Walshe. 3rd edition. Edinburgh, E. & S. Livingstone, 1943. 350 pages ; 46 illustrations. 15s. [£0.75]

An introduction to clinical neurology, for practitioners and students. It is a concise but comprehensive account of the commoner diseases of the nervous system, both organic and functional. The book first appeared in 1940, and received general approval. The third edition has been revised, and both text and illustrations have been augmented. A new section on pituitary neoplasms has been added, the chapter on injuries of the brain has been recast and expanded, and a short description of the pituitary-hypothalamus complex, with diagram, has been appended to the chapter dealing with anatomical or localising factors in diagnosis.

344/13

THE NATURAL DEVELOPMENT OF THE CHILD : A Guide for Parents, Teachers, Students, and others

by A. H. Bowley. 2nd edition. Edinburgh, E. & S. Livingstone, 1943. 184 pages ; 84 illustrations. 8s. 6d. [£0.425]

A brief account of the normal growth and development of the child from infancy to adolescence, with particular reference to emotional factors. It is written primarily for the student training to be a teacher, but it should also be of the utmost interest and value to parents, physicians, and all who, in various capacities, are concerned with the intellectual, emotional and physical welfare of the child. Valuable suggestions for further reading are included.

344/14

ILLUSTRATIONS OF REGIONAL ANATOMY

by E. B. Jamieson. 5th edition. 7 parts. Edinburgh, E. & S. Livingstone, 1944. 319 plates. £3.

This work consists of 319 anatomical plates, well produced in colour and bound in loose-leaf form. The whole production, which is of a high standard, is comprised in seven independent sections : central nervous system, head and neck, abdomen, pelvis, thorax, upper limb, lower limb. The work may also be obtained in a single bound volume.

344/15

THE QUEEN CHARLOTTE'S TEXT-BOOK OF OBSTETRICS

by Members of the Clinical Staff of the Hospital. 6th edition. London, J. & A. Churchill, 1943. 577 pages ; 294 illustrations. £1 5s. [£1.25]

Queen Charlotte's Maternity Hospital, the oldest maternity hospital in the British Isles, was founded in 1739. To-day it is the foremost hospital of its kind in Britain, and is an important centre for the training of obstetricians and midwives. This book, therefore, is written by a number of contributors whose experience is second to none. It sets forth the views held and the methods practised by those connected with the hospital. Since the first edition in 1927 the book has established itself as an important text for students of obstetrics. The latest edition has been carefully revised to include the most recent information on the subject, and has benefited by the addition of a small section on post-natal care.

344/16

SURGICAL NURSING AND AFTER-TREATMENT

by H. C. Rutherford Darling. 8th edition. London, J. & A. Churchill, 1944. 686 pages ; 210 illustrations. 12s. 6d. [£0.625]

As its title suggests, this book deals only with surgical nursing, but it may also be read with profit by the medical student during his time in the surgical wards. It includes a short account of the principles of pathology and bacteriology. A great deal of indispensable information is compressed into this relatively small book, which is well produced in spite of war conditions. It will serve as both textbook and reference book, and there is no doubt that this edition will prove as popular as its predecessors.

344/17

THE RADIOLOGY OF BONES AND JOINTS

by J. F. Brailsford. 3rd edition. London, J. & A. Churchill, 1944. 440 pages ; 404 illustrations. £2 5s. [£2.25]

The objects of this book are to provide a concise account of the bone changes seen in health and disease, to indicate the significance of the radiographic findings, and to present the recent advances which are recognised in radiological departments and journals but have not yet become incorporated in general textbooks. Illustrations of the commoner conditions are given, and an extensive bibliography is appended for the benefit of the reader who wishes to obtain special details and illustrations of any particular subject. Particular attention is paid to bone and joint changes resulting from trauma, the osseous dystrophies, tuberculosis, syphilis and neoplasm ; their interrelationship is a factor important to those concerned with rehabilitation. Consideration is given both to pathology and treatment of certain conditions of bones and joints, for, as the author points out, in some cases the treatment is indicated by the radiographic appearances, while in others the latter are changed as the result of treatment.

The radiographs have been carefully selected and their reproduction reaches the high standard one would expect to associate with an author of such standing among radiologists in Britain.

344/18

A SHORT PRACTICE OF SURGERY

by H. Bailey & R. J. McN. Love. 6th edition. London, H. K. Lewis, 1943. 1034 pages ; 922 illustrations. £1 16s. [£1.8]

The authors of this book have long enjoyed a reputation for presenting their subject in an easily readable manner. The work itself is a general survey of surgery, particularly suitable for the senior student and the general practitioner. The new edition has been thoroughly revised ; the book has always been notable for its illustrations and in this edition these have been enriched with over 40 additions, many in colour. Three new chapters deal with "Teeth and Gums," "Surgery of Parathyroid, Thymus, Adrenal Glands," "Urinary Symptoms, Genito-Urinary Investigations and Anuria." While this book cannot replace the larger and more detailed textbooks, its great virtue is that it presents the essentials of surgery in an attractive and easily assimilable form. It is one of the few books on general surgery that can be read from beginning to end by the student or practitioner.

344/19

ORTHOPÆDIC SURGERY

by W. Mercer. 3rd edition. London, E. Arnold & Co., 1943. 960 pages ; 415 illustrations. £2 5s. [£2.25]

A comprehensive survey of each branch of orthopaedic surgery, including the latest work. The technique of operations is given in sufficient detail to enable the young surgeon to perform them with confidence. The book was first published in 1932 and in

this third edition the author, who has had many years of practical experience in the subject, has taken the opportunity of incorporating new ideas, both from his personal experience and from the literature. Every chapter has been revised, and among the sections which have been re-written are those on circulatory disturbances, affections of the back, knee, shoulder and foot, and infections of the hand. A comprehensive bibliography is provided for further reading, and there is a full index.

344/20

MEDICAL BACTERIOLOGY

by L. E. H. Whitby. 4th edition. London, J. & A. Churchill, 1944. 342 pages ; 81 illustrations. 14s. [£0.7]

This book approaches the subject of bacteriology from the aspect most suitable to the medical student and the general practitioner who require only a knowledge of the essentials of the subject and their application to practical medicine. The book is, for this purpose, divided into two parts, "descriptive" and "applied," and the more common helminthic infections are also described. The subjects dealt with include the classification, variability, cultivation and staining of bacteria, theories of immunity, serological reactions, and details of the more common bacterial infections. This new edition has been augmented by the addition of a chapter on chemotherapy, whilst the sections dealing with the typhoid-coli group, diphtheria, gas-gangrene, filter-passing viruses and water analysis have been brought up to date.

344/21

A PRACTICE OF ORTHOPÆDIC SURGERY

by T. P. McMurray. 2nd edition, reprinted. London, Edward Arnold, 1944. 435 pages ; 191 illustrations. £1 10s. [£1.5]

A description of the basic principles of orthopædic surgery, particularly useful to the younger surgeon and the final-year student. Much of the original text has been rewritten and some new illustrations have been added.

The subject-matter is clearly set out and, with the illustrations, forms an excellent treatise on the subject. The author has had wide experience in this field and is careful to avoid too much detail and theory, which might confuse the reader. He has followed a systematic plan and includes differential diagnosis of the various conditions described. The types of treatment considered are those which in the author's experience have given the most consistently satisfactory results. The subject of fractures is wisely omitted, as being worthy of consideration in a separate volume, rather than as part of a book on orthopædics. The book is very well illustrated.

344/22

DEMONSTRATIONS OF PHYSICAL SIGNS IN CLINICAL SURGERY

by Hamilton Bailey. 9th edition. Bristol, John Wright & Sons, 1944. 351 pages ; 492 illustrations. £1 5s. [£1.25]

The author writes in his preface: "as physical signs may be likened to the laws of the Medes and Persians, it is not possible to state that a new edition of a book on this subject has been brought up to date." Nevertheless, this new edition of one of the most successful books on surgical diagnosis has been considerably revised as far as the illustrations are concerned. These have been of a high standard in previous editions and to improve upon them in this latest revision is proof of the author's ingenuity. Many are in colour and all succeed in their purpose of demonstrating the methods of physical examination and of eliciting the various signs diagnostic of disease.

The book has reached its ninth edition in 14 years and translations into several European languages have been published or are in preparation. Certain sections of the work have been revised; the interesting historical footnotes to most pages are retained.

344/23

VADE MECUM OF MEDICAL TREATMENT

by W. G. Sears. 4th edition. London, Edward Arnold, 1943. 388 pages. 10s. 6d. [£0.525]

A brief account of the essentials of treatment of diseases likely to be encountered in general practice is given in this book, which has, in earlier editions, already proved itself a useful guide for the senior student and the practitioner. The diseases are arranged alphabetically for quick reference, and the size of the book enables it to be carried in the pocket. It includes tables of doses, weights and measures and their conversion from and into the metric system, calorie values of foodstuffs, vitamin contents of foods, etc.

344/24

A HANDBOOK OF OPHTHALMOLOGY

by H. Neame & F. A. Williamson-Noble. 5th edition. London, J. & A. Churchill, 1944. 333 pages ; 235 illustrations. 18s. [£0.9]

This book is intended for medical students and general practitioners, and therefore is devoted mainly to a consideration of those diseases of the eye which are commonly met with in hospital out-patient practice. Brief descriptions of the less common conditions are given, and some space is devoted to an account of the usual methods of examination of the eye. In this new edition the section on inflammations of the conjunctiva has been largely re-written to incorporate details of the results of recent work on trachoma and the benefits obtainable by the wider use of the sulphonamides. The sulphonamides have fuller consideration in the chapter on Therapeutics. The relation of vitamins to ophthalmology is discussed at greater length than previously, and many other sections of the book have been revised and augmented. The illustrations are a notable feature of the book; those in colour are particularly well reproduced.

344/25

THE DIABETIC LIFE :

Its control by diet and insulin

by R. D. Lawrence. 13th edition. London, J. & A. Churchill, 1944. 251 pages ; 18 illustrations. 10s. 6d. [£0.525]

New editions of "The Diabetic Life" appear with such frequency that it has come to be regarded almost as an annual publication. Translations into French, Spanish, Dutch and Italian demonstrate still further the wide popularity of this book. Its main object is to be a practical guide in the treatment of diabetes, and this object it fulfils extremely well. As the author points out, the constant revision of a book tends to make it uneven; in this new edition he has therefore taken the opportunity of rewriting the text. The special difficulties of diabetics during wartime are provided for by a war-time supplement. This edition, like its predecessors, should prove invaluable not only to the doctor but also to the diabetic, whose intelligent co-operation is necessary for the best results.

Corrigendum

FRACTURES AND JOINT INJURIES

by R. Watson-Jones. 3rd edition. 2 vols. Edinburgh, E. & S. Livingstone, 1943. 960 pages ; 1353 illustrations. £3 15s. [£3.75]

In BMB 290/7 the number of illustrations in this work was incorrectly given as 745; the correct number is now stated above.

345

GUIDE TO THE JOURNALS

British Journal of Dermatology and Syphilis

56 : February 1944

Textile dermatitis. (J. H. T. Davies & A. N. Barker) 33-43

British Journal of Ophthalmology

28 : January 1944

Two cases of visible emboli in retinal arteries: with a histological study in one case. (W. E. C. Dickson, G. C. Pritchard, L. H. Savin & A. Sorsby) 1-14
Experimental corneal ulcers. (J. M. Robson) 15-25
A study of epithelial regeneration in the living eye. (I. Mann) 26-40
Ataxic nystagmus: A pathognomonic sign in disseminated sclerosis. (W. Harris) 40-42

28 : February 1944

Hereditary corneal dystrophy. (J. R. Mutch) 49-86
The value of ophthalmic treatment in the field. (G. C. Dansey-Browning) 87-97

28 : March 1944

War surgery of the eye. An analysis of 102 cases of intra-ocular foreign bodies. (H. B. Stallard) 105-135
Orbital cellulitis in a baby caused by acute osteomyelitis of the maxilla. (J. A. Magnus) 135-138
A wasp sting. (S. W. K. Norris) 139
Defective night vision among soldiers; dark adaptation results and their use in diagnosis. (I. C. Michaelson) 140-147

British Journal of Radiology

17 : March 1944

- The eye and radiology: Symposium. (J. F. Bromley, W. D. Wright & G. Spiegler) 65-69
Pneumoröntgenography of the knee joint. (P. P. Hauch) 70-74
The production of isodose curves and the calculation of energy absorption from standard depth dose data. (W. J. Meredith & G. J. Neary) 75-82
Venography in primary axillary vein thrombosis: Case report. (E. Samuel) 83-85
Some condenser ionization chambers for the measurement of x-ray dose. (C. W. Wilson) 86-89
The use of wedge filters in deep x-ray therapy. (F. Ellis & H. Miller) 90-94
Bone degeneration in the temporomandibular joint: Case report. (J. W. McLaren) 94-95
Medical uses of radium: Summary of reports from experimental research centres for 1942. 96-100

British Journal of Tuberculosis

38 : January 1944

- Tumours of the diaphragm: with report of a diaphragmatic cyst. (K. Robson & J. L. Colli) 3-6
Cardiac arrhythmia in bronchial carcinoma. (J. E. G. Pearson) 6-9
The management of pleurisy and pleural effusion cases. (F. R. G. Heaf & C. Hillingworth) 10-13
The clinical aspects of pulmonary tuberculosis in a community of aments. (J. F. MacMahon) 14-24
The life and discoveries of René Laennec. (C. Hoyle) 24-35

British Journal of Venereal Diseases

20 : March 1944

- Drug resistance in gonorrhoea with special reference to aetiology and treatment. (A. H. Harkness) 2-18
Is a new deal in the control of venereal disease necessary?—I. (I. N. O. Price) 19-21
Is a new deal in the control of venereal disease necessary?—II. (J. A. Burgess) 21-30
Sulphamezathine in gonorrhoea in the male: a report on fifty cases of gonococcal urethritis. (A. G. Johnson) 31-33
Acute encephalopathy during neosarsphenamine treatment: a report on six cases. (W. A. Young & S. Gordon) 34-36
Malarial treatment in the earlier stages of neurosyphilis. (F. G. Lescher & H. R. M. Richards) 37-41
Extensive tertiary syphilitic ulceration. (V. E. Lloyd) 42-44

British Medical Journal

1 : 19/2/44

- Some observations on hospital dust: with special reference to light as a hygienic safeguard. (L. P. Garrod) 245-247
A note on the transmissibility of haemolytic streptococcal infection by flies. (R. A. Shooter & P. M. Waterworth) 247-248
The Haldane haemoglobinometer. I. Iron, oxygen, and the British Standards Institution colour standard. (R. G. MacFarlane, J. R. P. O'Brien, et al.) 248-250
The haemoglobin equivalent of the B.S.I. Haldane standard. (E. J. King, M. Gilchrist & A. Matheson) 250-252
Cadmium poisoning. (P. Ross) 252-253
Dry blood test for typhus fever: preliminary report. (P. N. Bardhan, N. Tyagi & K. Boutros) 253-254

1 : 26/2/44

- Fainting in blood donors: Report to the Medical Research Council prepared by a Sub-committee of the Blood Transfusion Research Committee. 279-283
Pulmonary tuberculosis of bovine origin: with notes on bovine infection in three families. (L. J. Cutbill & A. Lynn) 283-285
Patch-testing in an East Coast town. (E. J. Simpson) 286-287
Sulphaguanidine in the treatment of Flexner dysentery. (H. G. Smith) 287-288
Haemolytic disease of the newborn: The preponderance of homozygous Rh-positive fathers. (G. L. Taylor & R. R. Race) 288-289

1 : 4/3/44

- Cranial-nerve palsies with herpes following general anaesthesia. (J. H. Humphrey & M. McClelland) 315-318
Hazards in the use of the closed-circuit technique for trilethal anaesthesia. (S. Carden) 319-320
Intelligence and season of conception. (J. A. F. Roberts) 320-322
Bacillary dysentery in Dundee: A comparative study of treatments. (W. M. Jamieson, J. Brodie & D. Stiven) 322-324
Meningococcal jaundice. (C. Crawford) 325

1 : 11/3/44

- Toxic effects in women exposed to industrial rubber solutions. (J. L. Hamilton-Paterson & E. Browning) 349-352
The sulphonamides in ophthalmia neonatorum. (A. Sorsby & E. Hoffa) 353-354
The blood pressure in midwifery. (W. Radcliffe) 354-358
Nervous breakdown in the Navy: Domestic difficulties as a factor. (G. Tooth) 358-360
The tonic action of strychnine. (W. F. Anderson) 360-361

1 : 18/3/44

- Hygiene aspects of the El Alamein victory, 1942. (H. S. Gear) 383-387
A study of a selected group of women employed on extremely fine work. (I. Mann & D. Archibald) 387-390
The action of electric blankets. (G. M. Brown & K. Mendelssohn) 390-392
Acute nicotinic acid deficiency (Anisicosis). (B. Gottlieb) 392-393
Chest screening in the ante-natal clinic. (R. Frank & A. L. Jacobs) 394

1 : 25/3/44

- Somatic manifestations of psychoneurosis. (I. Douglas-Wilson) 413-415
Lung abscess in relation to the influenza epidemic. (E. Davis) 416-417
Prognostic value of laboratory investigations in typhoid fever. (S. S. Bhatnagar) 417-419
Treatment of ocular infections with penicillin. (G. T. W. Cashell) 420-421
Control of very severe diabetes by a new arrangement of insulins. (R. D. Lawrence & W. Oakley) 422-423
Teaching and research in ophthalmology. (J. H. Parsons) 430-431

1 : 1/4/44

- Aetiology and treatment of convulsions during anaesthesia. (W. N. Kemp) 447-450
Hysterical sequelae of injuries. (P. D. Scott & P. Mallinson) 450-453
Chronic pulmonary catarrh in childhood. (A. B. Taylor) 453-455
Survey of vitamin C level in wartime in pregnant women. (A. A. Craig, F. J. W. Lewis & D. Woodman) 455-457
Sudden death in labour. (R. G. Cooke) 457-458

Edinburgh Medical Journal

51 : February 1944

- Koilonychia and polycythemia vera. (A. J. Glazebrook) 65-69
Symptomatic haemolytic anaemia: a report of four cases. (L. J. Davis) 70-83
Liver function in health and disease. (O. A. Trowell) 84 100
Tubercle bacilluria in the child. (W. T. Munro) 101-106

Journal of Mental Science

90 : January 1944

Special Number : Recent Progress in Psychiatry

- Introduction. (G. W. T. H. Fleming) 1-2
Mental Health Services—present and future. (A. A. W. Petrie) 3-16
Genetics in psychiatry. (E. T. O. Slater) 17-35
The anatomy of the nervous system. (W. E. Le Gros Clark) 36-53
Physiological psychology. (F. L. Golla) 54-63
Electro-encephalography. (W. G. Walter) 64-73
Biochemistry of the nervous system. (D. Richter) 74-94
Vitamin deficiency and the psychoses. (W. A. Caldwell & S. W. Hardwick) 95-108
Neuro-endocrine relationship. (M. Reiss) 109-126
Mental testing. (M. B. Brody) 127-151
Psychopathology. (S. M. Coleman) 152-192
Neuropathology. (A. Meyer) 193-230
Schizophrenia. (W. Mayer-Gross & N. P. Moore) 231-255
Depression. (A. Lewis) 256-265
Psychopathic personality. (D. Curran & P. Mallinson) 266-286
The psychoneuroses. (W. H. Gillespie) 287-306
Psychotherapy. (H. Crighton-Miller & G. H. Nicolle) 307-315
Arteriosclerotic, senile and presenile psychoses. (W. Mayer-Gross) 316-327
Psychiatric aspects of head injury. (E. Guttmann) 328-350
Neurosyphilis and its treatment. (W. D. Nicol & E. L. Hutton) 351-364
Child psychiatry. (E. M. Creak & B. J. Shorting) 365-381
Delinquency and crime. (W. N. East) 382-398
Mental defect. (L. S. Penrose) 399-409
Endocrinology in clinical psychiatry. (R. E. Hemphill) 410-434
Convulsion therapy. (J. C. Cook) 435-464
Insulin therapy. (I. Tennent) 465-485
Prefrontal leucotomy. (G. W. T. H. Fleming) 486-500
Legal aspects of psychiatry. (P. K. McCowan) 501-509

Journal of Obstetrics and Gynaecology of the British Empire

51 : February 1944

- The incidence of haemolytic disease of the fetus (erythroblastosis foetalis) in different families: The value of serological tests in diagnosis and prognosis. (K. E. Boorman, B. E. Dodd & P. L. Mollison) 1-23
A unique constructive operation. (V. Bonney & A. H. McIndoe) 24-29
The placenta in eclampsia and nephritic toxemia. (N. M. Falkiner & J. O. E. Apthorp) 30-37
Two unusual causes of intraperitoneal bleeding giving rise to collapse. (W. F. T. Hautain) 38-41
Pregnancy associated with congenital cystic disease of the lung. (J. P. Maxwell) 42-43
A case of retroperitoneal pelvic ganglioneuroma. (S. G. Clayton) 44-48
Epidemic encephalitis and pregnancy. (A. J. Hall) 49-50
Endocrine therapy in gynaecology and obstetrics: Critical review. (P. M. F. Bishop) 51-63

Journal of Pathology and Bacteriology

56 : January 1944

- The reaction of the pituitary gland and related hypothalamic centres in the hamster to prolonged treatment with oestrogens. (E. Vasquez-Lopez) 1-14
Mammary and testicular tumours in male mice of various strains following oestrogen treatment. (G. M. Bonser) 15-26
Hyaluronidase production by haemolytic streptococci of human origin. (N. Crowley) 27-36
Massive infection with intestinal anaerobic organisms as a cause of intra-pulmonary haemorrhage. (A. H. Cruickshank & J. I. Davidson) 37-48
The protective properties of pertussis antisera in experimental infection. (D. G. Evans) 49-54
The bactericidal power of guinea-pig serum on *H. influenzae*. (J. Gordon & K. Zinnemann) 55-60
Granulomatous arteritis in a lesion resembling sarcoidosis. (I. B. Gartside) 61-66
Malakoplakia of the urinary bladder. (J. E. Morison) 67-72
A diphyllorhynchium epidemic in trout. (J. B. Duguid & E. M. Sheppard) 73-80
The destruction of transfused erythrocytes in anaemia. (G. M. Brown, O. C. Hayward, E. O. Powell & L. J. Witts) 81-94
Observations on the photo-electric estimation of total haemoglobin. (E. B. Reeve) 95-108
Inclusion bodies in association with typhus rickettsiae. (A. M. Begg, F. Fulton & M. van den Ende) 109-114
The choroid plexus in the origin of tuberculous meningitis. (E. Stefan) 115-122
The in-vitro toxicogenicity and other characters of strains of *Cl. welchii* type A from various sources. (J. Keppie & M. Robertson) 123-132

Lancet

1 : 19/2/44

- Fractures of the femoral shaft: mechanics of reduction and fixation. (J. Charnley) 235-239
Accuracy of haemoglobin methods. (E. J. King, M. Gilchrist & G. E. Delory) 239-243
Early rehabilitation in abdominal surgery. (A. Shorter) 243-244
Acute necrosis of the liver: an unusual case. (E. R. Van Langenberg) 244-245
Peripheral arterial embolism. (L. W. C. Massey & P. Steiner) 245-247
Sulphapyridine anuria treated by unilateral renal decapsulation. (F. L. K. Lewis) 247
Aseptic cavernous sinus thrombosis with recovery. (H. S. Le Marquand & E. G. Recordon) 247-248

1 : 26/2/44

- Prevention of neonatal disease and death. (L. G. Parsons) 267-272
Prolonged post-traumatic amnesia: Findings at operation. (A. A. McConnell) 273-274
Hippuric acid liver-function test during treatment with arsenicals. (R. W. Riddell & T. E. Anderson) 275-276
Sulphamezathine in lobar pneumonia: A comparison with sulphapyridine. (G. Meltan) 277-278

1 : 4/3/44

- Penetrating wounds of the chest: Review of 291 cases in the Middle East. (W. F. Nicholson & J. G. Scadding) 299-323
Measurement of circulation time with saccharin. (F. P. Duran) 303-324

Penicillin in sulphonamide-resistant pneumonias, with special reference to staphylococcal infection and empyema. (T. I. Bennett & T. Parkes) 305-308
 Complications of trilete anaesthesia. (A. R. Hunter) 308-309
 Pneumoconiosis in boiler-scalers. (P. G. Todd & D. Rice) 309

1 : 11/3/44

Psychological medicine : Current methods of treatment. (I. Skottowe) 329-332
 Liver function after burns in childhood : Changes in lactulose tolerance. (S. L. Rae & A. W. Wilkinson) 332-334
 Agranulocytosis and aplastic anaemia after arsphenamines : Report of six cases. (James W. Ferguson) 334-337
 Sliding graft for ununited fracture of tibia. (B. H. Burns & L. S. Michaelis) 337-338
 Trypanosomiasis treated with pentamidine : a fatal case. (G. McComas, N. H. Martin) 338-339

1 : 18/3/44

Surgery in the field. (G. Blackburn) 361-365
 Absorption and excretion of sulphonamides in children. (M. W. Stanier & T. Stapleton) 366-367
 Confusional psychoses following sulphaguanidine therapy. (J. W. Crofton & G. Diggle) 367-368

Tobacco smoking and pulmonary complications after operation. (H. J. V. Morton) 368-370
 Extensive burns treated in an open irrigation chamber. (H. M. Goldberg) 371-372
 An unusual case of chronic meningococcal bacteraemia. (L. Martin & B. Dansie) 372
 The parachute surgical team. (C. J. Longland & L. Kessel) 381

1 : 25/3/44

Corneal vascularisation in nutritional deficiency. (T. K. Lyle, T. F. Macrae & P. A. Gardiner) 393-395
 Anaesthesia in fractures of the jaws. (R. P. W. Shackleton) 396-398
 Necrobacillosis in man. (G. B. Forbes & J. C. Goligher) 399-401
 Pathogenesis of sulphonamide neutropenia. (R. G. Park) 401-403

1 : 1/4/44

Surgery in the forward area. (W. A. Law) 425-429
 Prostigmin and ephedrine in myasthenia gravis. (A. Wilson & H. B. Stoner) 429-431
 Ocular signs of riboflavin deficiency. (W. J. W. Ferguson) 431-433
 Tropical eosinophilia. (B. G. Parsons-Smith) 433-434
 Implantation of testosterone in cast pellets. (P. M. F. Bishop & S. J. Folley) 434

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BRITISH MEDICAL BULLETIN

Vol. 2 (1944)

No. 5

SPECIAL CONTRIBUTIONS

BRITISH STUDIES ON THE GENETIC ASPECT OF DISEASE	
by Dr. Julia Bell	94
DEVELOPMENT OF OBSTETRICS IN BRITAIN	
by Professor J. Young	96
NUTRITION IN PREGNANCY AND LACTATION	
by Dr. W. C. W. Nixon	100
Bibliography on Maternal and Infant Nutrition	101

REVIEW OF SELECTED PAPERS

Drugs Acting on the Uterus	
Effect of Ergot on Uterine Involution	102
Uterine Response to Posterior Pituitary Lobe Extract	104
Effect of Gorse (<i>Ulex gallii</i>) on Uterus	104
Uterus-Relaxing Action of Raspberry-Leaf Extract	105

Pregnancy Toxæmia	
Vitamin B ₁ and Toxæmia of Pregnancy	105
Effect of a Pressor Posterior Lobe Extract in Normal and Toxæmic Women	105
Renal Failure after Utero-Placental Damage	106
Placenta in Eclampsia and Nephritic Toxæmia	107

Conception and Development	
Discussion on Causes of Sterility	107
Some Recent Investigations on Sterility	108
Intelligence and Season of Conception	108
Early Human Ova	108
A Study of Craniolacunias	109
New Light on the Origin of Craniolacunias	110

Nutrition : Lactation	
Diet in Reproduction and Lactation	110
Failing Lactation	110
A Lactation Reflex	111

Plastic Surgery	
A Unique Constructive Operation	111

Endocrinology	
Endocrine Therapy	112
Nomenclature of Hormone-Producing Ovarian Tumours	112

BOOKS, MEMORANDA, REPORTS	112
GUIDE TO THE JOURNALS	113

In No. 9 of Vol. 1 of the *Bulletin* appeared the first of a series of occasional articles on "The Development of Medical Studies in Britain." Two further articles of this series are published in this number.

Dr. Julia Bell, the author of one of these, was assistant to Karl Pearson from 1908–1914, and then studied medicine, returning to the Galton Laboratory in 1920 to work on human genetics. Later she became a member of the scientific staff of the Medical Research Council. She has been responsible for a series of elaborate studies on hereditary human diseases. These have been published in 9 parts of the *Treasury of Human Inheritance*, and she has published a number of shorter papers elsewhere. In 1941, Oxford University awarded the Weldon Prize and Medal to Dr. Bell in recognition of her biometric contributions to science.

Professor James Young, the author of the other article in the same series, was formerly Lecturer in Clinical Obstetrics and Gynaecology in the University of Edinburgh. He is now Professor of Obstetrics and Gynaecology in the University of London and has been Director of the Department of Obstetrics and Gynaecology at the British Postgraduate Medical School, London, since its opening in 1935. Professor Young is co-editor of the *Journal of Obstetrics and Gynaecology of the British Empire*, and is the author of a textbook of gynaecology which is now in its 6th edition.

Dr. W. C. W. Nixon was, until shortly before the war, Professor of Obstetrics and Gynaecology in Hong Kong University, and more recently has been consultant in the same subject to the London County Council. He is well known for his special interest in the preventive aspects of material and infant welfare, and in 1941 he gave the Blair Bell Memorial Lecture on "Diet in Pregnancy."

SPECIAL CONTRIBUTIONS

346

THE DEVELOPMENT OF MEDICAL STUDIES IN BRITAIN: II. THE GENETICAL ASPECT OF DISEASE

JULIA BELL, M.A., F.R.C.P.

Scientific Staff, Medical Research Council

As long ago as 400 B.C. Hippocrates, writing on epilepsy, tells us:

"Its origin is hereditary, like that of other diseases. For if a phlegmatic be born of a phlegmatic and a bilious of a bilious and a phthisical of a phthisical and one having spleen disease of another having disease of the spleen, what is to hinder it from happening where the father or mother were subject to the disease, certain air offspring should be so affected also?"

Similar examples might be cited from early medical literature demonstrating the recognition of the hereditary nature of certain diseases by the exceptional men of the day. For readers for the most part appear to have turned a blind eye to the facts and concentrated their attention upon dealing with the consequences, even as so many men and women of our countries, in their often short-sighted efforts at humanism, do to-day.

But again, there are always exceptional men who try to point the way. Thus Plato writes:

"The shepherd or herdsman, or breeder of horses, or the like, when he has received his animals will not begin to train them until he has first purified them in a manner which befits a community of animals; he will divide the healthy and unhealthy, and the good breed and the bad breed, and will send away the unhealthy and badly bred to other herds, and tend the rest, reflecting that his labours will be vain and without effect either on the souls or bodies of those whom nature and ill-nurture have corrupted, and that they will involve in destruction the pure and healthy nature and being of every other animal if he neglect to purge them away. Now the case of other animals is not so important; they are only worth mentioning for the sake of illustration, but what relates to man is of the highest importance and the legislator should make enquiries and indicate what is proper for each in the way of purification and of any other procedure."

More commonly, the attitude adopted in the face of hereditary defect has been that illustrated by Pierre Guillemeau in 1585:

"... comme chose née avec la personne ne se peut amender, n'estant besoin d'y mettre aucun remède."

Aristotle, too, has something to say:

"Of a certainty the germ cell is both originator and controller of this child from that parent; these things lie in its nature and thus it must develop. Empedocles erred when he said that many of the characters of living forms arise through their environment during development. . . . For man generates man and the special characters of the parent determine the same characters in the offspring."

Nineteenth Century: Mendel, Galton and Pearson

We see, then, that the potency of heredity was recognised at a very early age, but little more was achieved until the nineteenth century, when the significance of pedigrees of

disease began to be investigated and the varied mechanism of heredity to be considered. The sex-linked nature of hæmophilia and of colour-blindness was pointed out and the characteristic method of descent came to be described as Nässe's Law (1820), Lossen's Law (1877) or Horner's Law (1876), after each of these authors had described their respective observations. Later in the century was a period of great awakening. The discovery of Mendel's work, with the enunciation of his laws, led to the birth of Mendelism and to experimental genetics, and Francis Galton arose to urge the need for the study and control of factors which impaired national efficiency, and to bring about the birth of the science of eugenics (a term which was originated by Galton).

"The world is beginning to awaken to the fact that the life of the individual is in some real sense a prolongation of those of his ancestry. His vigour, his character and his diseases are principally derived from theirs,"

writes Francis Galton, and if he had forerunners—as e.g. Shakespeare:

"Let those whom Nature hath not made for store,
Harsh, featureless and rude, barrenly perish"—

it was Francis Galton who first realised the urgent necessity for the collection of facts as a basis for the study of the potency of heredity, and envisaged the mathematical nature of the problems involved in their interpretation. Galton's main interests, though of wide scope, were focussed on the question of the preservation and development of those characters which make for racial fitness—in particular those of mental ability and physical fitness—rather than on any detailed study of the genetical aspects of disease. There can be little doubt, however, that his work provided the stimulus for the stream of work on human genetics which has gone steadily forward since his day.

Possibly much that issued from the fertile brain of Francis Galton would have aroused only temporary interest in a select group of scientists of his day, if the great ability and enthusiasm of Karl Pearson had not appeared in the field to develop methods of enquiry and point the way to the analysis of observations and to the facts which can and cannot be deduced from them. Francis Galton founded the Galton Laboratory of Eugenics, attached to *University College*, London, and endowed the first Chair of Eugenics for the furthering of research in the subject. Karl Pearson, at Galton's special request, occupied this Chair during the years 1911–33, combining with this new department his previously established Biometric Laboratory and his organisation for statistical research. R. A. Fisher succeeded Karl Pearson as Galton Professor of Eugenics in 1933.

Karl Pearson's work was of such wide scope that it is impossible to describe in any detail even the small section of it

which is concerned with the subject of this paper, but I think he would agree that his concern was primarily in the development of a statistical technique, and in the insistence on its application to all fields of science, including genetics. He ever urged the need for the accumulation of facts on an adequate scale as the basis of knowledge, and he designed *The Treasury of Human Inheritance*, the prime purpose of which should be to provide a collection of pedigrees upon which the geneticist could test out his theories. Fierce battles ensued between the experimental geneticists, who claimed to have demonstrated the validity of Mendelism, and Karl Pearson with his followers, who would test their figures and retort that on the basis of probability their observations presented very heavy odds against the applicability of Mendel's laws.

On the one hand, Karl Pearson was something of a watch dog, always alert against the perpetuation of error through the then widespread lack of knowledge of statistical technique; on the other hand, he worked ceaselessly to add to positive knowledge concerning the potency of heredity and the relative strengths of nature and nurture. He obtained a measure of heredity as evidenced by observations of such characters as physical measurements, standards of health and of ability in parents and offspring or in pairs of siblings. Environmental effects were determined by correlating a great variety of conditions—to mention one example only, the state of nutrition and mental capacity in school-children. His conclusions invariably showed the greatly preponderant importance of heredity and the folly of concentrating exclusively on the improvement of environment.

Thus, commenting on the differential fall in the birth rate since 1877, he writes:

"The man and woman who cannot afford to marry are now taxed for the education, the sanitation, the medical provision and, very often, the nutrition of the offspring of those who ought not to marry."

Yet Karl Pearson never minimised the value of environment and the duty of society to see that the genetic potentialities of the individual are given all possible aids to their development, always remembering that improved environment alone cannot involve steady racial progress.

Another piece of work of national importance achieved under the direction of Karl Pearson was Snow's demonstration of natural selection at work in man; it appeared from the material then available that a reduction of infant mortality led to a higher death rate among the young children who survived; in other words, important though it is to safeguard the life of every child born, one cannot expect in this way to compensate for the reduction of the birth rate in the fitter and abler sections of the community.

Karl Pearson's most prolific period was before the 1914-18 war; his conclusions were often unwelcome and roused hostile reactions in many quarters; they are there for all to ponder on, and surely the need to do so was never greater than in planning now for our post-war years.

Later Nineteenth and Early Twentieth Centuries

If, then, the first period of our survey is characterised by the observation and sometimes the recording of the sequence of events, the second period, focussed in the nineteenth and early twentieth centuries, is notable for (a) a great stride forward in the development of controlled experimental work among plants and animals, and the consideration of the application of knowledge thus learned to human problems; (b) the organised search for facts bearing on human heredity and its control, with the development of methods to provide a measure of the significance of observed characters and their relative potency in the population concerned. There was now brought to the fore the conception of prediction and the control of events within the limits imposed by man.

There were many notable pioneers in the field during this period—Bateson and his school, Morgan, Lamarck, Weissmann, de Vries and Johannsen, to mention a few only. If this brief survey appears to concentrate largely upon the pioneer work of Francis Galton and Karl Pearson, it is not only because the writer had exceptional opportunity of observing their work and the stimulus it provided during some thirty years. The work then done provided a firm foundation of fact and many pointers for the next generation of investigators to pursue.

Laboratories and Literature

During this period the Galton Laboratory had been established; the John Innes Horticultural Station too, had been endowed, with Bateson as its first Director, and much pioneer work in experimental genetics was begun. Departments of similar or more specialised scope have been multiplied in recent years in the Universities of London, Oxford, Edinburgh, and elsewhere. Publications in England, started during this period, include the *Journal of Genetics* (1910-), published in Cambridge, and, under the direction of Karl Pearson, *Biometrika* (1901-), *Annals of Eugenics* (1925-), *The Treasury of Human Inheritance* (1909-), together with a long series of monographs under (i) *The Biometric Series*, (ii) *Studies in National Deterioration*, and (iii) *Eugenics Laboratory Memoirs*. At the end of this period, some thousands of pedigrees of disease had been worked out and embodied, for reference purposes, in collections of histories from the literature, in which the three main genetic types are clearly defined and illustrated.

Modern Human Genetics

The third period of our survey, reaching to the present time, has proved so fertile and is so full of promise for the future that it is possible only to indicate very briefly and inadequately some of the lines upon which modern geneticists are working. The age has given evidence of great originality of thought and method and it is difficult to set any bounds to the possibilities arising from the converging paths of the geneticist, the embryologist and the physiologist under such direction as that given by Goldschmidt in America and by Joseph Needham and Waddington in England.

British work on human genetics has been primarily led by R. A. Fisher, J. B. S. Haldane and L. Hogben, with notable contributions from the clinical side by E. A. Cockayne and L. Penrose. A fundamental feature of the period has been the very fruitful conception of the gene as the carrier of hereditary characters with its localisation in the chromosome, and the observation of the phenomenon of linkage, when two hereditary characters are so related that they tend to occur—or fail to occur—together in individuals of a stock. Among the pioneers in these lines of investigation were Correns, Bateson with his co-workers, Morgan, and Sturtevant. Although the nature of the hypothetical gene is still unknown, the influence and location of its function has been determined to such a degree of accuracy in certain primitive forms of life that they have become plastic material in the hands of the breeder who can, on the basis of his hypotheses, build up populations of a specified variety, predetermine its character, and test out his theses.

All this work has a limited application to the much more complicated problems of hereditary disease in man, but a notable start has been made in the demonstration of linkage in a number of families carrying two sex-linked diseases, namely, colour-blindness and hæmophilia. The first pedigree illustrating this phenomenon was published by Madelener; later, more conclusive evidence of linkage was found in England after a systematic search initiated by Haldane. Further examples of linkage in man are due to Riddell, Birch, White, and Burks. Methods of investigating the question of linkage have been initiated and elaborated primarily by Bernstein, R. A. Fisher, and J. B. S. Haldane. Taking a long distance point of view, this line of enquiry carries great possibilities. It may contribute to the localisation of particular genes on chromosomes, or perhaps enable one to detect the presence of a harmful gene before its effects are manifested and thus reassure the normal members of affected stocks and point the way for potential carriers to avoid the birth of defective offspring.

Perhaps the most important single discovery bearing on human heredity during the modern period has been the identification of the genetics of blood group membership. It is a sufficiently potent fact that we are able under certain conditions to state that a particular child was not the offspring of its alleged parents on the basis of a blood group examination; it is thought that, as more blood group factors are detected, the scope of their revelations may provide perhaps the most hopeful line of advance in the knowledge and control of human heredity. The chief advocate of this pursuit in England, following the pioneer work of Todd, has been R. A. Fisher, with his colleague G. L. Taylor; preliminary work has been done in the standardisation of methods and technique, but the work has been inevitably curtailed owing to the

demands of war ; much of interest may be looked for in this direction on the restoration of peace.

The collection of pedigrees of disease continues and it is now recognised that in few conditions can the mode of inheritance be said to be invariable. It is perhaps safe to say that red-green colour-blindness and hæmophilia are due to sex-linked genes located on the *X* chromosome, or that Huntington's chorea and blue sclerotics are caused by dominant genes in that they become manifest in heterozygotes ; it is, however, impossible to say anything of the genetic sources in a case of, e.g. pseudo-hypertrophic muscular dystrophy, or *retinitis pigmentosa*, without a knowledge of the family and personal history of the individual concerned. Just as it has come to be recognised that a particular gene can lead to multiple effects and in certain cases the sequence of events can be reconstructed (see e.g. Bonnevie, 1934 ; Grüneberg, 1938-40), so it can be seen that indistinguishable clinical appearances may arise from different genes carrying a quite different outlook for the individual, the age of onset of the disease and prognosis for the patient varying markedly with the observed method of descent in the family. The writer has been responsible for the authorship of nine issues of the *Treasury of Human Inheritance* since 1922, including some 2,000 pedigrees of anomaly or disease in the eye or in the nervous system, and can testify to the often marked variability in the manifestation of a particular hereditary disease from one family to another, as well as the tendency to close resemblance in all the characteristics of the disease, whether genetic or clinical, in members of the same stock.

Multiple cases of disease in the same family are not necessarily conclusive evidence of a hereditary basis when the condition is common in a population ; thus the detection of a genetic basis in phthisis, some types of cancer, diabetes mellitus, peptic ulcer, etc., may become a very difficult problem complicated by such environmental factors as exposure to infection, lowering of resistance, liability to strain or subjection to excitants. With regard to phthisis, the work of Karl Pearson and his associates was very suggestive of the importance of the genetic basis ; if this factor is masked by more conspicuous environmental effects, as evidenced by increased incidence under war conditions, its potency has been confirmed by investigations into the occurrence of the disease in pairs of like and of unlike twins. This method of investigation, based on the consideration that genetic characters would be found more commonly in both twins of like type than in those of unlike type, originally suggested by Francis Galton, has been much developed of recent years in a de-

liberate search for the resemblance in twins of each category, particularly so in the work of Hogben, Dahlberg, Percy Stocks and von Verschuer. It provides perhaps the most hopeful line of investigation into the hereditary basis suspected in some types of cancer. Much suggestive experimental work however is being done by such workers as Furth in America and Gorer in Britain, on the leukaemias and cancer in mice, which have valuable applications to human problems. An interesting summary of investigations along these lines has been published recently under the authorship of J. Engelbreth-Holm (1939).

If, as we must agree, it is not possible to stay the onset or course of disease or defect genetically determined, a good deal of consideration has been given to its possible prevention by such measures as the discouragement of consanguineous marriage, or the sterilisation of potential transmitters. With regard to the former, the first-cousin marriage-rate among the parents of in-patients of the General Hospitals in England and Wales, determined with the aid of the *Medical Research Council* (Bell, 1940), was found to be 0.606 % of marriages only ; the dangers possibly inherent in such marriages are undoubted, and extreme caution in undertaking them should be practised by the individual, but at their present low rate little gain can be expected from their discouragement in the population as a whole. Dahlberg (1939) reports similar low consanguinity rates among marriages in European countries.

The voluntary sterilisation of defectives or of those deemed to be potential transmitters of hereditary defect, though undoubtedly often humane in its scope, may be very wasteful in operation ; too often we do not know the potential transmitter, as such, until he has produced his defective offspring. Certain individuals should certainly abstain from parenthood, but from the genetic standpoint it is unlikely that much gain could be expected to follow from restrictive measures of this nature.

The output of work in experimental genetics and embryology recently described by Joseph Needham, *Sir William Dunn* Reader in Biochemistry in the University of Cambridge, is almost overpowering in its many-sided implications to workers outside that special field. The line of investigation is obviously of very great promise, but we need to be cautious in applying conclusions arrived at by work on relatively primitive organisms to the highly evolved mechanisms of man. Is it not probable that natural selection has carefully protected the human developing embryo from environmental effects and from the fingers of meddling man ?

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THE DEVELOPMENT OF MEDICAL STUDIES IN BRITAIN : III. OBSTETRICS

JAMES YOUNG, M.D., F.R.C.S., F.R.C.O.G.
British Post-Graduate Medical School, London

The earliest authentic landmark in the history of British midwifery dates from the reign of Henry VIII. In 1540 there appeared the first textbook of midwifery to be printed in England. This was a translation of *Der Swangern frauen*

und hebammen rosgarten written by Eucharius Rösslin and published in Hagenau in 1513. This book, the first devoted to midwifery after the discovery of printing, was translated into the various European languages and into Latin (1532).

The English translation was made from the Latin text under the title *The Byrth of Mankynde*. It passed through many editions, the last appearing in 1676. The translation of the first English edition is commonly ascribed to Thomas Raynalde, but his name does not appear in the book until the edition of 1545. Richard Jonas claims to have translated the 1540 edition, which was "imprynted at London by T. R." This "T. R." was no doubt the well-known printer Thomas Raynalde. Later editions appeared under the editorship of Thomas Raynalde, Physician. Ballantyne has made a careful study of this point and gives full details in his paper (1906).

From a perusal of this famous book we obtain a clear light on the art of midwifery during the sixteenth and seventeenth centuries. In the English translation there has been a free revision of the original text; later editions include anatomical plates from Vesalius. Despite this, the book essentially retains its original form and it demonstrates how the teaching in regard to normal and abnormal labour was still largely based upon the work of Soranus and the Alexandrian school of the first and second centuries A.D.

Throughout the sixteenth and seventeenth centuries British midwifery exhibited little progress. Its practitioners were for the most part ignorant and illiterate midwives who, in times of emergency, had recourse to the doctor with his destructive instruments, more especially the hook. It is true that there were important movements on the Continent, especially in France, where the great surgeon Ambroise Paré had in 1550 rediscovered the value of podalic version in cases of difficult delivery; this, although known by the ancients, had apparently been forgotten for nearly fifteen centuries. From this discovery, and the French school which began with Ambroise Paré, may be dated the rise of modern obstetrics. At a time when Continental travel was fashionable it is likely that this rising French School had some influence on British thought, but there is little record that this was immediate and it was not until 1634 that Ambroise Paré's works were translated into English.

It was about this time that a member of the Chamberlen family in England (probably Peter Chamberlen the Elder, who died in 1631) invented the obstetric forceps. This, although one of the greatest and most beneficent of all obstetrical discoveries, had little immediate influence on the art as, for over a century, in keeping with a practice common to those days, it remained a close family secret. Indeed the use of forceps did not become general until Chapman published his description in 1713.

William Harvey's Contribution

It is not generally appreciated that the first original work on midwifery by an English writer was the chapter "De partu" in the *Exercitationes de Generatione Animalium* of William Harvey (1578-1657), the discoverer of the circulation of the blood. This appeared in 1651 and was translated into English in 1653. In the improved translation of Harvey's works carried out for the Sydenham Society by Willis (1847) the "Motion of the Heart and Blood" occupies 141 pages, whilst the "Anatomical Exercises of the Generation of Animals" occupies 444 pages. Harvey's contribution to obstetrics is not to be measured by the degree in which it advanced the art and practice. It is to be found rather in the new intellectual spirit which it reveals. Authority is displaced by science and observation, and the extent to which this implied a massive revolution in thought may be gauged by the fact that we find Harvey constantly making his peace with Hippocrates, Aristotle and Galen. There can be found no more convincing commentary on the barrenness of the long intervening centuries than a study of Harvey's work.

It is against this background that we can best appreciate the significance of Harvey's contribution. The greater part of the book is devoted to a long series of experiments and observations on the development of animal ova and on the anatomy and physiology of the foetus. The short chapter (*de Partu*) on parturition makes it clear that Harvey had a considerable experience in practical midwifery. The book, however, does not claim to enunciate any great new principles in the obstetric art, and for this reason the claim made by Aveling that Harvey should be regarded as the Father of British Midwifery is hardly to be justified. It is somewhat strange to find that although Fabricius, Harvey's teacher, had taught that the child is born as the result of the muscular action of the womb, Harvey still held stubbornly to the

ancient view that "it is the foetus itself which, with its head downwards, attacks the portals of the womb, opens them by its own energies and thus struggles into day." The head is "situated superiorly and the face usually turned towards the back of the mother. A short time, however, before birth the head is bent downwards towards the orifice of the uterus and the foetus, as it were, in search of an outlet, dives to the bottom." It is also interesting to find the persistence of the ancient doctrine that "the cartilaginous attachments of the pelvic bones so lose their rigidity that the bones themselves yield readily to the passage of the foetus and thus greatly increase the area of the hypogastric region."

It is about this time that we first learn of efforts made to raise the standard of the training of the midwives. Harvey and his contemporary and friend, Percivall Willughby (1596-1685) referred in strong terms to the manner in which women in labour suffered at the hands of untrained midwives. They both emphasised that labour was a physiological process and that "the midwife's duty in a natural birth is no more but to attend and wait on Nature." Several members of the Chamberlen family also interested themselves in plans for the improvement of the status of midwives and it would seem that, as the result of the mediation of the College of Physicians, some control was imposed and improved instruction made available. But progress was slow and throughout the seventeenth, eighteenth and nineteenth centuries the ignorant and unskilled midwife remained as a persisting reproach to British obstetrics.

We have previously referred to the important school of obstetrics which had arisen in France. By the end of the seventeenth century its influence was great. Its chief exponent was François Mauriceau (1637-1709), whose *Traité des maladies des femmes grosses*, 1668, was translated by Hugh Chamberlen (1673) and thus made available for English readers. This book was the first textbook of obstetrics in the modern tradition and it had a marked influence on British thought and practice. English editions continued to appear till 1752.

Eighteenth Century : Beginnings of Modern Obstetrics

The rise of modern British midwifery dates from the eighteenth century. It was during this century that the obstetrical forceps, hitherto a closely guarded family secret, was introduced into common use. It is from this period that this instrument takes its effective place beside podalic version as one of the most beneficent discoveries in medicine. Together, these procedures in the hands of the scientifically trained man-midwife were destined more and more to displace the mutilating and dangerous operations of former days and, at the same time, to wrest from the woman midwives the monopoly which they had so long enjoyed. It was during this century that the anatomical and clinical discoveries of William Smellie and others revolutionised the science and art of midwifery. Smellie and a great band of contemporary workers and writers—Deventer (Holland), Maubray, Giffard, Manningham, Pugh, Chapman, Fielding Ould, William Hunter, Denman and White—broke the last fetters which still bound the obstetric art to traditionalism and obscurantism. It was during this century, also, that the first professorship of midwifery was instituted in Edinburgh in 1726 and that, with the establishment of the first lying-in hospitals in England, Scotland and Ireland, the care of pregnant and labouring women entered on a new phase and the basis was laid for the proper instruction of the doctor and the midwife.

The most noteworthy development in the art of midwifery sprang from the increasing emphasis on the essentially physiological nature of ordinary labour and on the importance of the avoidance of interference until the indications for this were clear. So much dominated by the physiological outlook on labour was the British School of Obstetrics that Böer was at a later date to declare that he "learnt in France what Art, in England what Nature could do." Throughout the century this is a main theme running through the many British books on midwifery which now began to appear. In the hands of Giffard, Pugh, Chapman and Smellie in Britain and of Levret in France, the forceps underwent gradual evolution from the rather crude implement of the Chamberlens to the modern fenestrated instrument with the pelvic curve and the convenient English or Smellie lock. The study of pelvic anatomy led to clearer understanding of the phenomena of labour and the objective study of the process of delivery led for the first time to a knowledge of the "mechanism" of labour.

Influence of William Smellie

The progress which was now taking place in England was so great and so rapid that this country had by the middle decades of the eighteenth century established for itself a position of leadership. The outstanding figure in this obstetrical galaxy was William Smellie (1697–1763), who has been justly described by Fasbender as “one of the most important obstetricians of all times and countries.” He was born in Lanark in Scotland, practised there for some years after graduating M.D. at Glasgow University on February 18, 1745. In 1739 he studied under Grégoire in Paris and thereafter during the whole of his active life he lived in London, where he built up the first important school of midwifery and altogether 900 pupils attended his courses. In 1759 he returned to Lanark where he died in 1763. Apart from the great influence of his personal teaching and example, his place in obstetric history is secured by his great *Treatise on the Theory and Practice of Midwifery* published in 1752, followed in 1754 by a second volume consisting of a *Collection of Cases*. The *Collection of Preternatural Cases* appeared posthumously, in 1774, as the third volume. In 1754 he published *A Set of Anatomical Tables* which, according to another great obstetrician, Michaelis, “have perhaps achieved more in the spread of correct ideas of labour than all the books which have ever been written on the subject.” Smellie’s *Treatise* possesses an additional literary interest in that it was prepared for the press by Tobias Smollett, the great English novelist, who was a close personal friend of the author. The work passed through at least nine editions in English and it was translated into French, German and Dutch. In 1876–78 it was reprinted by the New Sydenham Society under the editorship of McClintock.

The *Treatise* reveals throughout the qualities which distinguished Smellie’s personality and work—the originality of his genius, which illumines everything which he touches, his close and careful clinical observation, his shrewd and critical judgment, his modesty and his honesty of purpose. One of the book’s greatest claims to distinction is that it is almost alone amongst obstetric works of a bygone age in that it is still studied by obstetricians with profit and inspiration. It began a new era and marks out Smellie as the father of modern obstetrics. As Fairbairn so aptly says “it is interesting to note that the date of his birth, 1697, is but twenty-one years, and the publication of his epoch-making treatise on midwifery but sixty-six years, after the appearance of the last edition of the *Byrth of Mankinde* (1676), which was merely a rehash of the teaching of the great Alexandrian school, thus showing the long reign of the ancient and the almost sudden appearance of modern obstetrics.”

Opposition to Man-Midwives

With the rapid development of the science and art of midwifery leadership passed inevitably into the hands of the male midwives and this created difficulties with the female practitioners. From ancient times it had been an accepted convention that attendance on women in labour was a woman’s function. It had not been regarded as in any way falling within the sphere of the doctor, save in those instances where the midwife had failed by her own efforts. Only then was he brought often secretly into the labour room in an effort to save the life of the mother which, if possible at all, could often be achieved only by destructive manipulations on the child. There was thus added to the sense of impropriety and even indecency of the male doctor in the labour room the feeling that his presence too often was a harbinger of death and disaster. There would seem to be no doubt that in England these views regulated the attitude of the public mind towards midwife and doctor well into the eighteenth century. It is true that before this period there are a few recorded instances of court “accoucheurs.” Thus Peter Chamberlen attended Queen Henrietta Maria in 1628 and Hugh Chamberlen delivered the future Queen Anne in 1692. In France, also, Boucher attended La Vallière, the mistress of Louis XIV, in 1663 and Clément attended Madame de Montespan in 1670 and the Dauphine in 1682, and it is said that male midwifery tended from this time to become more fashionable in France. On the Continent there does not seem at any time to have existed the acute rivalry which, with the rapid development of the male practitioner, was due to break out in England. This arose from the fact that on the Continent the woman midwife’s position was more secure from the beginning. We know, for example, that from the

seventeenth century French midwives had a lying-in hospital (the *Hôtel Dieu*) set aside in Paris for their training, and that this was supported by visiting male accoucheurs. We also know that in Holland and Denmark schools of instruction for midwives supported by the State existed from an early date. At various times there emerged from these Continental schools midwives who gained for themselves an important place in history. Louise Bourgeois was a distinguished midwife of the seventeenth-century French school and Justine Siegemundin of the eighteenth-century German school. Two later French midwives of distinction were La Chapelle and Marie Boivin. The last-named (1773–1841) gave the first accurate description of hydatid mole. Whilst on the Continent there had been created a body of trained, disciplined and self-respecting midwives, in England, at the time of which we speak, the midwives were untrained except for the instruction which they picked up at random. We have seen that attempts had been made at varying times to improve their status and their training but it is doubtful if these achieved much. It thus happened that when in the eighteenth century the man-midwives began to engage wholesale in, and to lay down the principles for, practice in a field over which women had hitherto exercised a virtual monopoly the women practitioners were filled with dismay. A wordy storm broke out through the usual medium of these days, the pamphlet. The pamphleteers, irate midwives with some sympathising medical men, hurled their protests, often in very intemperate language, at the heads of the male practitioners. Smellie received more than his share of this outburst, his chief opponent being a Mrs. Elizabeth Nihell, who described him as a “great horse-god-mother of a hemidwife”! A staple argument was that the passing of midwifery into male hands would expose labouring women to unnecessary and dangerous interference and the wholesale employment of barbarous instruments.

This squabble between the woman- and man-midwives is unimportant except in so far as it serves to throw light on influences which determined the future of British midwifery. It was a time of great progress when male and female midwife, both essential in their own sphere, might by their combined efforts have built up an effective organisation similar to that growing up in Continental countries. Instead, by their estrangement the hands of the clock were put back for a century. It is true that the setting up of lying-in hospitals provided new facilities for the training of female midwives. But throughout a great part of the nineteenth century the midwife remained too often the degraded type drawn by the novelist and caricaturist of the times. Indeed it is only recently (Midwives Act, 1902) that we finally saw the passing of the untrained “handy-woman,” on whom so many of our countrywomen depended for their sole aid during their confinement. This schism between the male and female midwives was destined during the eighteenth and nineteenth centuries to spread its influence beyond these shores. Carried over to America, the tradition persisted. To this day, in the United States of America, the attitude of the male practitioner towards the female midwife has often remained one of thinly veiled contempt at a time when, in Great Britain, she has been reinstated in a position of prime importance in the maternity organisation of the country.

Nineteenth Century : Anæsthesia and Control of Sepsis

British workers played a notable part in the two great developments of the nineteenth century, the discoveries in relation to anæsthesia and puerperal sepsis. It was Simpson (1811–1870) who first introduced anæsthesia into obstetrical practice and thus opened out the road to new surgical progress and adventure in this country. He communicated his first paper on chloroform to the Medico-Chirurgical Society of Edinburgh on March 10, 1847.

The contagious nature of puerperal sepsis had been suspected by several workers before Pasteur. Thus Gordon of Aberdeen in 1795 published a treatise demonstrating the relation between puerperal fever and erysipelas, whilst fifty years later and almost at the same time (1843) Oliver Wendell Holmes in America and Semmelweis in Vienna built up a solid argument for the contagious origin of the disease. But it was not until Pasteur’s dramatic intervention in a discussion at the French Academy on the causes of puerperal fever in 1867, when he suddenly rose from his seat, walked to the blackboard and drew for his audience the chain streptococcus that he had obtained from the discharges and from

the blood of infected women, that the proof was final. On the foundation of Pasteur's work Lister (1827-1912) built up antiseptic, which later merged into modern aseptic, surgery. The greatest immediate effect was seen in the prevention of the massive epidemic scourges which from the time of their first development in the eighteenth century had remained a constant menace of the lying-in hospitals. In the final development of the technique directed to the prevention of obstetric contagion a notable part has been played by British bacteriologists. Smith of Aberdeen (1933) and the Colebrooks at the *Bernhard Baron* Research Laboratory attached to *Queen Charlotte's* Hospital in London (1936) demonstrated that a main source of this contagion was the upper respiratory passages of the attendant nurse or doctor. From these discoveries has sprung the modern technique of the labour room, including the face mask. Leonard Colebrook has also played a major part in proving the efficacy of the sulphonamide drugs in the treatment of puerperal sepsis due to the hæmolytic streptococcus. For the five years 1931 to 1935 the respective case mortality rates for puerperal sepsis at *Queen Charlotte's* Hospital were 31·6 %, 21 %, 20·6 % and 24·4 %. During January to August, 1936, after the introduction of prontosil, the death-rate in 85 cases infected by hæmolytic streptococci dropped to the low figure of 3·5 % (Colebrook & Kenny, 1936). The work of these investigators was an important factor in the considerable reduction in the maternal mortality rates of this and other countries during recent years and, by its proof of the value of sulphonamide therapy, it has exercised a wide influence in general medicine and surgery.

Organisation of Midwives

An important event in the history of British obstetrics was the establishment of the Central Midwives Board under the Midwives Act, 1902. The Board is now under the administrative control of the Ministry of Health. It is responsible for the admission to the register of midwives and for framing rules for their training and practice, and it possesses considerable disciplinary powers. Local supervising authorities for the purposes of the Midwives Acts, 1902-1936, are the councils of counties and of county boroughs, who are responsible for the inspection of midwives, with powers to suspend a midwife from practice if such a step appears necessary to prevent the spread of infection. One of the most important consequences of the new Acts is that no woman may use the title of midwife unless certified under the Acts and no one, unless certified, may attend women in childbirth otherwise than under the direction and personal supervision of a registered medical practitioner. By this step there has been finally secured the elimination of the untrained woman who throughout the centuries had been a grave reproach on British obstetrics. A further more recent step (1936), which has helped to fill a serious gap in the maternity services, is the statutory obligation of every local supervising authority to make arrangements for the adequate provision of whole-time salaried midwives for their area.

Twentieth Century and Earlier : Preventive Aspects

In the field of preventive medicine as applied to maternal and child health Great Britain has played a leading rôle. Ballantyne (1861-1923) directed attention to the great importance both to mother and child of a periodic and careful medical supervision carried out throughout pregnancy, and his work led to the foundation of the modern antenatal clinic. Newsholme (1857-1943), Chief Medical Officer of the Local Government Board, was at about the same time drawing attention in a series of notable official memoranda to the influence of social and economic factors on the high infantile morbidity and mortality of these days. The combined efforts of these and other pioneers led to the passing of the Maternity and Child Welfare Act, 1918. By the Notification of Births Act, 1907, notification of births to the local authority had been adoptive and had enabled the authority to extend medical and auxiliary services to nursing and other mothers. In 1915, notification of births was made compulsory and the local authorities were empowered to undertake maternity and child welfare work. These earlier and tentative provisions were extended and coordinated under the Act of 1918 and the Public Health Act,

1936. By these acts every welfare authority must appoint a maternity and child welfare committee. As a consequence there has gradually grown up during the past 25 years a service, or series of services, by which the mother can secure from public sources skilled supervision for herself throughout the antenatal, the lying-in and the postnatal period, and for her child up to school age. In England and Wales these services now (1943) include 1,651 antenatal clinics and 2,893 infant welfare centres. Their continuing expansion is seen in the fact that, whilst during 1936 the percentage of expectant mothers who attended antenatal clinics in England was nearly 49, during 1942 it had reached 70. An important feature of the services is the free provision of supplementary food (milk and vitamin preparations) for expectant and nursing mothers of poor economic circumstances.

During recent years there has been a marked decline in maternal mortality. In England and Wales the rate, which remained stubbornly high over a long period, has fallen from 4·21 per 1000 births (live and still) in 1932 to 2·47 in 1942. This considerable fall is in the main due to a diminution in the deaths from sepsis (from 1·61 per 1,000 births in 1932 to 0·42 in 1942). Since the beginning of the twentieth century there has been a remarkable and steady decline in the infantile mortality rate—from 154 per 1,000 live births in 1900 to 49 in 1942.

Recognition of Obstetrics and Gynæcology as a Specialty

Throughout its history until quite recent times obstetrics has had to contend with the indifference and often the open hostility of the teaching schools and universities and the medical corporations. These schools and corporations, controlled by physicians, for long were as jealous of the man-midwives as of the surgeons, and by their efforts to retain the obstetric practice of the doctor within their own close monopoly they often actively boycotted these practitioners and discouraged their efforts at progress. We have seen that midwifery received academic recognition in Scotland early in the eighteenth century. In England this recognition was slow and it was not until the passing of the Medical Act, 1886, that the doctor was required to pass an examination in midwifery for qualification. But the training of the student in obstetrics remained for long in an unsatisfactory state. It was only after the issue of the Interim Report of the Departmental Committee on Maternal Mortality and Morbidity in 1930 that this question for the first time received serious consideration. Thereafter the *General Medical Council*, in consultation with the Licensing Bodies, issued recommendations which have resulted in an expansion of the training facilities, including a compulsory period of residence by the student in an obstetric hospital. By these measures and, where necessary, by collaboration between the teaching school and a local authority hospital, with the object of increasing the available clinical material, the standard of instruction has been greatly improved.

With the foundation in 1929 of the British College (now the Royal College) of Obstetricians and Gynæcologists, midwifery in Britain has at last established for itself its just place in the medical triad. The College contains, at the time of writing, 234 Fellows (F.R.C.O.G.), 475 Members (M.R.C.O.G.) and 354 Diplomates (D.R.C.O.G.). Fellows, apart from Foundation Fellows, are elected from such Members as are judged by the Council to have advanced the science and art of Obstetrics and Gynæcology in such a way as to merit promotion. Members are admitted after examination, and they must have been entered for at least three years on the British Medical Register or "be eligible for entry thereon in virtue of being entered on the Register of duly qualified medical practitioners of a Commonwealth, Dominion, Union, State, Colony or Dependency forming part of the British Empire." Every applicant for membership must have held the following resident appointments in a recognised hospital: six months in general medicine or surgery, six months in obstetrics and six months in gynæcology. He must submit complete records of 25 selected and personally conducted obstetric and 10 gynæcological cases, with two commentaries, one obstetrical, the other gynæcological, each limited to 2,000 words. After the acceptance of his case-records and commentaries, he is permitted to sit for the examination (written, clinical and *viva voce*). The Diploma is "designed to assist the public authorities and committees of voluntary hospitals and other

organisations in the selection of practitioners who have made a special study of obstetrics after qualification." The applicant must have held resident appointments in a recognised hospital as follows: six months in general medicine or surgery and six months in obstetrics. He must submit evidence of adequate experience in antenatal, postnatal and infant welfare work and in gynaecology.

Gynaecology

Gynaecology is a creation of the nineteenth century. The scientific study of the diseases of the female generative organs dates from the development of modern pathology—from the work of Virchow and the investigation of disease processes by means of the perfected microscope. In the building up of the pathologico-clinical basis of nineteenth century gynaecology, a leading part in Britain was played by Simpson, Lawson Tait and Matthews Duncan. Abdominal surgery was born in 1809 when McDowell of Kentucky carried out his first ovariectomy; by 1830 he had performed the operation upon thirteen women, and of these at least eight are known to have survived. It was not, however, till the advent of anaesthesia and antiseptic surgery that operative gynaecology began its advance on a broad front. In this phase Spencer Wells (1818–1897) first firmly established the place of ovariectomy and Lawson Tait (1845–1899) the wider possibilities of pelvic surgery. The first successful operation for ruptured tubal pregnancy was carried out by Lawson Tait in 1883. The first systematic text-book on gynaecology of the modern type was published in Edinburgh by Berry Hart and Freeland Barbour (1884).

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Scientific Advances

During more recent years British workers have played an important part in the rapid evolution which has taken place in physiology and pathology in relation to obstetrics and gynaecology and in the application of these sciences in the field of diagnosis and treatment. The employment of posterior pituitary extract as an oxytocic drug by a distinguished British obstetrician, W. Blair Bell (1909), is an early landmark in the application of endocrinological discovery to practical medicine. The recent discovery by Dodds and his co-workers (1937 and 1938) of the synthetic oestrogens of the stilbæstrol group (stilbæstrol and hexæstrol) is an important British achievement in the sphere of sex endocrinology. These synthetic products have been proved to possess in a high degree the physiological properties of the biological oestrogens and they have established for themselves a primary rôle in the treatment of the female menopause, in the inhibition of lactation, where this is required in the puerperium, and in other ways. They possess two outstanding advantages, their cheapness and their activity when administered orally. In the obstetric field the clinical observations of Chassar Moir (1932) culminated in the isolation of ergometrine (Dudley & Moir, 1935), the water-soluble alkaloid which is believed to be responsible for the traditional clinical effect of ergot. These investigations have succeeded in clearing up the ambiguity which long surrounded the ergot alkaloids and they have added a valuable oxytocic drug to the obstetrician's equipment.

In the preparation of this article the author has freely consulted the writings of Professor John Glaister and the late Professor Herbert R. Spencer.

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348

PRACTICAL APPLICATIONS OF KNOWLEDGE OF NUTRITION TO PREGNANCY AND LACTATION

W. C. W. NIXON, M.D., F.R.C.S., F.R.C.O.G.

lately Professor of Obstetrics and Gynaecology, Hong Kong University

There is now abundant evidence that pregnancy and lactation are dietetic strains. These physiological states in a woman's life are in fact "diet efficiency" tests. During these periods of stress, border-line states of nutrition are sometimes revealed which otherwise would have remained latent. For example, the effects of drain upon maternal calcium are seen in the form of adult rickets. Furthermore, the babies of such women may themselves be rachitic (Maxwell, Lin & Kuo, 1939). That pregnancy is a dietetic stress can also be seen from the fact that during the last trimester the mature foetus has received 75 % of its weight of protein, 93 % of fat, 65 % of calcium, 68 % of phosphorus, 80 % of iron (Huggett, 1942). During this period, 70 % of its total birth weight has been deposited. Again, during lactation there is a marked drain on the maternal tissues. The nursing mother requires for every pint [about 568 cm.³] of breast milk about 24 g. of good quality protein in food in addition to her other daily protein requirements. Of calcium she needs three times as much as the non-pregnant woman, and of iron an increase of 60 %. Calorie requirements in late pregnancy are 2660 daily in contrast to 3220 in lactation.

There is no doubt that the better the nutrition during pregnancy, the more likely is lactation to be satisfactory. In

a community where diet is faulty or restricted it is the mothers, expectant and nursing, and the children who will suffer first.

Mass Dietetic Treatment of Pregnant Women

Recently four large-scale field investigations have been undertaken which have shown the benefit of proper feeding in pregnancy:

- i. The *National Birthday Trust Fund* distributed between April 1934 and March 1939 special foods to expectant mothers in certain areas in South Wales and the North of England. The results of this supplementary feeding of 11,618 women have now been reviewed (Balfour, 1944). There were 8,095 women who acted as controls. Each woman on the *Birthday Trust* register received the following once a fortnight: either a 4-ounce [about 112 g.] carton of "Marmite"¹ or similar yeast extract, or, as an alternative, an 8-ounce [about 230 cm.³] bottle of "Minalex."²

¹ MARMITE (*Marmite Food Extract Co.*). A yeast extract, said to be rich in vitamin-B complex.

² MINALEX SYRUP (*Glaxo Laboratories*). Each fluid ounce [about 28 cm.³] contains vitamin A 18,000 international units, vitamin D (calciferol) 3,000 international units, iron and ammonium citrate 13½ grains [about 0.86 g.], calcium glycerophosphate 2 grains [about 130 mg.], potassium glycerophosphate ½ grain [about 13 mg.], sodium glycerophosphate ¼ grain [about 6 mg.], manganese glycerophosphate ¼ grain [about 2.6 mg.], copper sulphate ¼ grain.

It is estimated that the amounts supplied were sufficient to give the women each day 240 international units of vitamin B₁ or 13,500 international units of vitamin A and 2,250 international units of vitamin D.

The conclusions reached were that there was a significant reduction in the stillbirth and neonatal mortality rates of the fed group as compared with the controls. Maternal deaths in the series were too few for any conclusions to be drawn.

ii. The Toronto feeding experiment has received much attention (*British Medical Journal*, 1943). In this, a group of expectant mothers was given the following daily supplements: 40 ounces [about 1136 cm.³] milk; 1 ounce [about 28 g.] cheese, 1 egg, "an average serving" of butter and meat; two servings of vegetables in addition to potato; 1 orange or half a grapefruit or 5 ounces of tomato juice; one half of the cereals and bread were consumed in whole-grain form; 2 teaspoonfuls [about 8 cm.³] of codliver oil or concentrated equivalent; liver once a week, iodized salt or medicinal iron was used if indicated, 2 tablespoonfuls [about 28 cm.³] of wheat-germ daily.

Women on a poor diet acted as controls. Those who received the above supplements had a reduction of threatened and actual miscarriages, premature births, stillbirths and toxæmia of pregnancy. Their babies also had less colds, pneumonia, rickets and anaemia. Breast feeding in hospital and at home was possible in a greater number of these women.

iii. *The People's League of Health* was founded by Miss Olga Nethersole in 1917. Its purpose is to improve the standard of health both in the community and in the individual citizen, and it has striven to effect these ends by the collection and distribution of knowledge. The *League* has stimulated and co-ordinated research and spread this knowledge among the general body of the people. The many subjects in which it has interested itself include safe milk, tuberculosis, bread, mental welfare, etc. An investigation was conducted between March 1938 and the end of 1939 (*British Medical Journal*, 1942). It was based upon observations on 5,000 expectant mothers attending 10 London hospitals. One half of these women received supplements of calcium, iron, iodine and vitamins A, B, C, D before the 24th week of pregnancy. These were continued until delivery. The most significant findings were the reduction of prematurity and toxæmia of pregnancy.

These findings are important for two reasons: (i) by reduction of prematurity, infant mortality would be lowered, as 50 % of infantile deaths under one month are due to prematurity, (ii) by reduction of toxæmia (1.8 % in the treated group) it is estimated that, on the basis of the annual number of births (approximately 600,000 in the immediate pre-war years in England and Wales), there would be 10,000 fewer cases of toxæmia in the year.

iv. Utheim-Toverud (1939) at a rural health centre in Norway was able to reduce prematurity and toxæmia of pregnancy and to improve lactation by the proper feeding of expectant and nursing mothers. There was a marked diminution in the incidence of rickets among the children of those women who attended the centre. Utheim-Toverud emphasises the importance of oranges and cod-liver oil in the maternal diet, with supplements of iron if indicated.

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British Medical Journal (1942) 2, 77

British Medical Journal (1943) 1, 16

Huggett, A. St. G. (1942) *Pharm. J.* 148, 21

Practical Measures for the Improvement of Maternal Nutrition

i. *Food Advice Bureau*. One of the primary functions of workers in maternity and child welfare clinics is the supervision of diet. By establishing a Food Advice Bureau in the waiting-room of the clinic, mothers can be instructed as to what to buy, how to buy, and what to do with the food when bought. Such a bureau was established by the writer (Nixon, 1942) at the *Soho Hospital for Women*, London, in 1941. Other hospitals have since started similar bureaux, and this service is proving most popular. It is essential that the demonstrator should prepare the food in front of the women. She should discuss their feeding problems in a simple and practical way. The mothers make notes, ask questions, taste the food and collect Ministry of Food recipes, until it is their turn to be examined by the doctor. The demonstrator should act as an adviser, and not as a teacher of the academic kind. The ideal would be to have communal feeding at the clinic. Women of the poorer classes, particularly those of younger years, are only too willing to be educated in health matters when these are explained simply and the benefits that accrue to them and their babies are emphasised by a doctor or a nurse. It is for this reason that the Food Advice Bureau should be linked with the antenatal and postnatal clinics.

ii. *Distribution of dietary supplements*. In Britain, the Ministry of Food has wisely taken control of the distribution of food. By its priority and rationing schemes expectant and nursing mothers and children have extra milk, eggs and meat. From the clinics can be obtained orange juice and cod-liver oil. In this way these important population groups are being protected from the effects of war-time restrictions of food.

iii. *Elimination of nutritional anaemia*. Mackay, Wills, Dobbs & Bingham (1942) have brought forward evidence, that anaemia in babies is in part the result of anaemia in their mothers during pregnancy. Anaemia in an expectant mother should be corrected before she starts labour. There are many clinics now in which iron is prescribed as a routine during pregnancy. It is difficult in war-time to estimate the hæmoglobin of every pregnant woman, and the alternative is to give iron. Ferrous sulphate tablets is the usual form in which it is administered.

Nutritional anaemia is a common cause of poor health in women and children and results in lack of mental and physical vigour. It is a disease that can be prevented by means which are obvious, namely, proper feeding.

Diet has become one of the most important aspects of public health and nutrition has become a social obligation as important as sanitation, education and the relief of destitution. All those responsible for the health of expectant and nursing mothers must interest themselves in the practical aspects of diet. By precept and example, the elementary principles of proper feeding can be inculcated. In this way the mothers can be guided so that they themselves will contribute to one of the greatest measures in public health—proper nutrition.

Mackay, H. M. M., Wills, L., Dobbs, R. H. & Bingham, K. (1942) *Proc. roy. Soc. Med.* 36, 69

Maxwell, J. P., Lin, H. A. C. & Kuo, C. C. (1939) *Proc. roy. Soc. Med.* 32, 287

¹ Nixon, W. C. W. (1942) *J. Obstet. Gynec.* 49, 614

Utheim-Toverud, K. (1939) *Acta paediatr., Stockh.* 24, 116

¹ [see BMB 108]

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[The following is a list of selected recent works in the English language on various aspects of nutrition in pregnancy and infancy.]

Bourne, G. (1942) *Wartime food for mother and child*, London

Burke, B. S., Beal, V. A., Kirkwood, S. B. & Stuart, H. C. (1943) Nutrition studies during pregnancy. *Amer. J. Obstet. Gynec.* 46, 38-52

Diet histories were obtained from 216 middle-class women who were examined periodically throughout pregnancy and puerperium. Diets of 31 were rated as excellent or good, and 13 of the infants of this group were "superior" compared with 1 out of 36 whose mothers had poor diet. Total number of "superior" infants was 23, and of this group 56 % of the mothers had excellent or good,

35 % fair, and 9 % poor prenatal diets, compared with 3 %, 13 % and 79 % respectively for the mothers of the 33 poorest infants.

Ebbs, J. H. (1942) The incidence and mortality of breast- and artificially fed infants admitted to hospital with infections. *Arch. Dis. Childh.* 17, 217-219

Examination of records of 1,500 hospitalized infants in Toronto showed that fewer breast babies were admitted with infection than artificially fed babies. The incidence of breast-feeding among the 1,500 admissions was less than half that among the healthy babies attending the city clinics.

Ebbs, J. H. (1943) Handbook of nutrition. 21. Nutritive requirements in pregnancy and lactation. *J. Amer. med. Ass.* 121, 339-345

A review of data relating to the nutritive requirements in pregnancy and lactation. Includes an extensive bibliography.

Ebbs, J. H., Brown, A., Tisdall, F. F., Moyle, W. J. & Bell, M. (1942) The influence of improved prenatal nutrition upon the infant. *Canad. med. Ass. J.* 46, 6-8

Ebbs, J. H. & Kelley, H. (1943) The relation of maternal diet to breast feeding. *Arch. Dis. Childh.* 17, 212-216

Poor mothers supplied with extra food both pre- and postnatally were more successful in nursing their infants than mothers left on poor diets.

Ebbs, J. H., Scott, W. A., Tisdall, F. F., Moyle, W. J. & Bell, M. (1942) Nutrition in pregnancy. *Canad. med. Ass. J.* 46, 1-6

Ebbs, J. H., Tisdall, F. F. & Scott, W. A. (1941) The influence of prenatal diet on the mother and child. *J. Nutrit.* 22, 515-526

Impressive change followed doubling or trebling of vitamin B₁ intake in women who had been on a poor diet. It is claimed that many of their minor complaints disappeared, and that mental attitude improved.

Garry, R. C. & Stiven, D. (1936) A review on recent requirements in pregnancy and lactation, with an attempt to assess human requirements. *Nutr. Abstr. Rev.* 5, 855

It was found that the weight of the newborn infant was not influenced by the maternal diet unless there were extreme deficiencies. Full bibliography.

McCance, R. A., Widdowson, E. M. & Verdon-Roe, C. M. (1938) A study of English diets by the individual method. III. Pregnant women at different economic levels. *J. Hyg. Camb.* 38, 596-622

It was found that the lower the income, the lower was the intake of animal protein and vitamin-containing foods.

Mackay, H. M. M. (1941) Calorie requirements of full-term and premature infants in the neonatal period. *Arch. Dis. Childh.* 16, 166-181

A formula is suggested whereby the food intake of new-born babies may be regulated. According to this, the baby should receive on the first day calories equivalent to $\frac{1}{3} \times 50 \times$ birth-weight in pounds ($\frac{1}{3} \times 110 \times$ birth-weight in kg.), and his feeds should increase by this same amount each day of the first week, so that by the 7th day he would be given 50 calories per pound (110 calories per kg.) birth-weight.

Mackay, H. M. M., Goodfellow, L. & Hill, A. B. (1931) Nutritional anaemia in infancy. The influence of iron deficiency on infant health. *Spec. Rep. Ser. med. Res. Coun., Lond.* No. 157

Showed that there was a lower haemoglobin level in every month of the first 18 months of life in infants born of anaemic mothers than of infants born of mothers without anaemia.

McNeil, C., Capon, N. B., Collis, W. R. F., Graham, S. & Moncrieff, A. (1943) Neonatal mortality. *Arch. Dis. Childh.* 18, 54-56

Report of a sub-committee of the *British Paediatric Association*. It recommends that breast milk should be available for every infant; if the mother cannot provide it, breast milk pools should be available. More of these should be set up in maternity hospitals, etc. The diet of the mother is an important factor; among the poorer classes extra food should be provided to ensure a well-balanced diet.

Maxwell, J. P. (1932) Vitamin deficiency in the antenatal period, its effects on the mother and the infant. *J. Obstet. Gynec.* 39, 764-776

Among pregnant women in China there appeared to be an association between lack of vitamin A and puerperal sepsis.

Mellanby, M. (1934) Diet and the teeth. III. Effect of diet on dental structure and disease in man. *Spec. Rep. Ser. med. Res. Coun., Lond.* No. 191

Deficiencies in antepartum diet are regarded as an important factor in dental caries appearing in the child.

Mellanby, M. & King, J. D. (1939) Vitamins and dental caries. *Ergebn. Vitamin u. Hormonforsch.* 2, 1-54

The association of rickets, dental caries and lack of vitamin D is shown. The value of a substantial increase in daily consumption of fresh dairy produce, especially milk, by pregnant women and by children, would do much to eliminate dental disease.

Neale, A. V., Cassie, E., Braid, F. & Pierce, M. (1943) Breast feeding in relation to female labour as it particularly affects Birmingham. *Arch. Dis. Childh.* 18, 59-64

The results of an investigation on breast feeding in 1937 Birmingham babies born in 1941 and 2,698 born in 1942. Wartime conditions have not materially altered the incidence of breast feeding; few women are prepared to go to work while the baby is under 6 months. Percentage of babies breast-fed for at least 3 months was 53 in 1941 and 52 in 1942. Breast feeding was discontinued because of the mother going out to work in 11 % of cases.

Nixon, W. C. W. (1938) Oedema in pregnancy. *J. Obstet. Gynec.* 45, 48-59

It is suggested that an interrelation exists between vitamin deficiency, the endocrine system and the condition of toxæmia of pregnancy. For marked oedema 50-100 cm.³ of a 50 % solution of glucose intravenously is recommended; if the condition is considered due to vitamin B₁ deficiency, this vitamin must be given, preferably subcutaneously or intravenously in severe cases.

Robinson, M. (1941) A comparison of breast-feeding in ten classes of the population. *Arch. Dis. Childh.* 16, 31-34

When all classes of the population are considered over a long period, there is no real decline in breast feeding, but during 1930-39 there was a real decline in three social groups, the greatest occurring in the first month among the wives of labourers. Continued poverty lowers the ability of the mothers to keep the baby on the breast throughout the first month.

REVIEW OF SELECTED PAPERS

Drugs Acting on the Uterus

350

AN INVESTIGATION OF THE EFFECT OF ERGOT ALKALOIDS IN PROMOTING INVOLUTION OF THE POSTPARTUM UTERUS

by C. Moir & C. Scott Russell, *Journal of Obstetrics and Gynaecology of the British Empire*, 50, 94-104, April 1943

In this paper from the *Nuffield Department of Obstetrics & Gynaecology*, Oxford, the authors first review the history of the medicinal use of ergot.

Ergot and its Alkaloids

Ergot of rye administered by mouth stimulates uterine contraction. This fact was known as far back as 1582. Its use, however, by the medical profession dates from 1808 when the *New York Medical Repository* published a letter by Dr. John Stearns in which he praised the value of a decoction of ergot powder for hastening lingering parturition. Following this lead, the medical profession quickly accepted the new drug, using it sometimes wisely, but often dangerously, as contemporary writings show. Before long the "*pulvis ad partum*" was renamed the "*pulvis ad mortem*": it had become evident that the "incessant and urgent" uterine contractions stimulated by incautious use of the drug could lead to foetal asphyxia or even to rupture of the uterus. These were bitter experiences, but the lesson was well learned, and at the present day ergot is not given in normal cases till after expulsion of the foetus.

In 1906 Barger and Dale isolated and described ergotoxine, and at an early date Dale discovered that the alkaloid was capable of counteracting the effects of sympathetic stimulation.

In 1918 ergotamine was isolated by Stoll. More recently, the senior author of the present paper showed (Moir, 1932) that crude ergot extracts, which had been regarded by pharmacologists as inert, had a definite action on the puerperal uterus. Further investigations resulted in the isolation of a new alkaloid to which the name "ergometrine" was given by its discoverers (Dudley & Moir, 1935; Dudley, 1935). In the U.S.A. the name ergonovine was applied to the new alkaloid, which is also marketed under several trade names.

Though five alkaloids of ergot have been isolated and no less than fourteen molecular complexes described, the active alkaloids can be simply arranged. There is, on the one hand, the group represented by ergotoxine and ergotamine. These alkaloids are very sparingly soluble in water, are slow to act, especially if administered by mouth, but, once absorbed, are rather persistent in effect. If given in excess, they produce various toxic symptoms, notably the peripheral gangrene which characterises chronic ergot poisoning. Standing in sharp contrast is ergometrine. This alkaloid is readily soluble in water, is remarkably quick in action even if given by mouth, and is non-toxic in dosage greatly exceeding that used in clinical practice.

These alkaloids have the effect of stimulating powerful contractions in the uterus at first of short duration but following each other in such rapid succession that the uterus as a whole has no time to relax and a state of spasm prevails. Later, as the effect diminishes, individual strong contractions alternate with intervals of relaxation.

Uses in Obstetrics

There are two main uses of ergot in obstetrics. One is to stimulate uterine activity in cases of postpartum hæmorrhage; the other is to promote—so it is supposed—the involution of the postpartum uterus. For the first indication, the value

of the drug has been amply proved: for the second indication, uncertainty regarding its usefulness still prevails. The present authors report fresh observations on the rate of involution of the postpartum uterus and the possible influence of repeated ergot administration.

Effect on Height of Puerperal Uterus

Some years ago (1936 & 1937) patients delivered at the *British Postgraduate Medical School* (Hammersmith Hospital) were divided into 3 groups in order to determine whether ergot therapy would influence the involution of the uterus. The patients in the 1st group were given ergometrine 0.5 mg. by mouth 3 times daily for the 1st week of the puerperium. Those in the 2nd group received ergotamine ("femergin") 1 mg. 3 times daily by mouth for a similar period, and those in the 3rd group were observed as controls. From 589 case records that were found suitable for analysis, the height of the uterine fundus above the symphysis pubis on the 2nd, 4th, 6th, and 8th days was noted and the arithmetical means for the 3 groups of patients were obtained. The standard deviations in all 12 sub-groups lay between 0.6 and 0.8 inch [1 inch = 2.54 cm.].

By subtraction, the average involution of the uterus in successive 2-day intervals was obtained; the difference between corresponding figures in the 3 groups never exceeded 1/10 of an inch.

These findings were of considerable interest; they were, however, open to the serious criticism that the measurements had not been made by one observer throughout. It was, therefore, decided that further and more accurate measurements should be made. This latter investigation was made in the *Radcliffe Infirmary*, Oxford. The subdivision of cases was similar to that used in the earlier experiment, but to ensure, as far as possible, that the bladder and rectum were empty, each patient had received special preparation. On the 2nd morning an enema was given and the height of the uterus was measured immediately after the bowel and bladder had been emptied. On the 3rd night an aperient was given, followed by a further enema next morning unless the bowel had already been satisfactorily emptied. The bladder was again emptied immediately before the uterus was measured. The same preparations were made before the 3rd measurement. If there was any suspicion that either the bladder or rectum had not been emptied, the patient was considered unsuitable, and the readings were discarded.

Four difficulties quickly became apparent. The first 3 pertained to the measurements, the last to the condition of the bowel and bladder.

i. It is impossible to measure the height of the uterus above the symphysis pubis more accurately than to the nearest $\frac{1}{4}$ inch; to obtain even this precision a thin subject is necessary. In some cases the uncertainty amounts to nearly 1 inch.

ii. The uterus can be moved downwards or upwards in the abdomen, sometimes by as much as 1 inch.

iii. Towards the end of the 1st week of the puerperium the uterus, in some cases, tilts backwards; it is then more difficult to measure its height than it was in the early days of the puerperium.

iv. It is not always possible to be certain that the bowel and bladder have been completely emptied, however carefully the patient has been prepared. The last-mentioned difficulty is illustrated by a chart showing the distortion of the uterine involution curve by the varying fullness of the rectum.

Comparison between the average height of the uterus on successive 2-day intervals showed a similar rate of involution in the 3 groups. These observations, therefore, did not give any support to the usual belief that ergot, administered over a period of days, hastens uterine involution.

Effect on Lochia

The effect of ergometrine and of ergotamine on the amount and character of the lochia was also studied. Consecutive normal cases were divided into 3 groups as before. All discarded sanitary pads were placed by the nurses in special bowls and examined personally at approximately the same hour each morning. Over 100 cases were recorded.

It was soon discovered that some women after childbirth hardly soil the sanitary pads, most of the lochia escaping when a bed-pan is used for the purpose of emptying the bowel

or bladder. Examination of the pads alone may thus give an entirely false impression of the amount of lochia passed. The co-operation of the nursing staff was, therefore, obtained, and each time a bed-pan was used an entry was made on a special chart recording whether the lochial discharge was absent, scanty (small clots), moderate (medium clots), or profuse (large clots). While this arrangement had the disadvantage that the charts were filled by different observers each day, it was a decided improvement on the methods employed in any previous investigation of which the authors have knowledge. From the pads personally inspected and the special charts kept by the nursing staff, a reasonably reliable record of the amount and character of the lochia passed during the previous 24 hours was obtained.

The following guarded conclusions were drawn:

- i. The normal variation in the quantity and character of the lochia is very great.
- ii. The practical difficulties in collecting all the discharge and in estimating its amount are so numerous that, unless wide variation is constantly observed, records of lochial discharge do not give any trustworthy indication of the effect of drugs on the uterus.
- iii. Administration of ergometrine did not produce any constant change in character or quantity of the lochia.
- iv. Administration of ergotamine ("femergin") did not produce any constant change in character or quantity of the lochia.

Discussion

The authors then discuss briefly certain recent papers (Der Brucke, 1935; Davis, Adair & Pearl, 1936; Kushner & Wahrsinger, 1938; Lounsbury, 1940) purporting to support the long-held view that ergot administration promotes uterine involution. In all the examples they believe that the claims made have not been substantiated. In no case does it appear that the difficulties of the investigation had been fully appreciated, nor is there evidence of adequate safeguard against the inclusion of fallacious recordings.

Involution should be regarded, not as the disuse-atrophy of an unwanted organ, but as a physiological process requiring an unimpeded blood supply. If at any stage of the puerperium activity is forced on the uterus, the steady involution of that organ may well be hindered, for an active muscle does not atrophy. The ergot alkaloids bring about a series of contractions so rapid that the uterus as a whole has no time to relax. Each muscle-fibre is, however, performing many times its previous amount of work. It is a mistake to suppose—as is sometimes done—that ergot causes the uterus to become firm in an inactive or static sense. Uterine muscle is not leather in a tanner's vat: it is living tissue, and a "firming" is the result of greatly increased work of muscle-fibres.

Those who prescribe a course of ergot to patients suffering from puerperal uterine infection do so in the twofold belief that the drug will check any tendency to sub-involution, and that it will expel infected material from the uterine cavity. In patients presenting symptoms of uterine sepsis, pathogenic organisms are living and multiplying in the uterine wall, and mere contraction of the organ will not get rid of them. Violent activity may, on the contrary, disseminate infection. It is a cardinal rule that all inflamed organs should be kept at rest, and if this is the correct treatment for, say, a septic finger, it is difficult to understand why matters should be reversed for a septic uterus. Further, if by the uterine contraction the blood supply is appreciably reduced, there will also be a diminution of the supply of leucocytes, of natural antibodies, and, on occasion, of chemotherapeutic substances. Ergot therapy may thus have a harmful influence.

Conclusions

The long-held belief that continued administration of ergot favourably influences the course of uterine involution receives no support from the investigations reported in this paper. The practice of giving the drug throughout the puerperium appears to arise from an imperfect understanding of the nature of the uterine involution on the one hand, and of the mode of action of ergot on the other. There is little doubt that vast quantities of this drug are daily used for purposes that may fairly be described as wasteful, useless, and possibly even harmful. At this time of international

stress, importation of ergot is in many countries difficult and uncertain; there is, therefore, urgent need to conserve the existing supplies of this essential drug.

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351

THE RESPONSE OF ISOLATED MUSCLE-STRIPS FROM THE UPPER AND LOWER SEGMENTS OF THE HUMAN FULL-TIME PREGNANT UTERUS TO PITRESSIN AND TO PITOCIN

by C. Scott Russell, *Journal of Obstetrics and Gynaecology of the British Empire*, 50, 287-298, August 1943

Though the vasopressor and the uterus-stimulating (oxytocic) activities of the posterior lobe of the pituitary have long been known, there is still doubt as to whether the posterior lobe contains one or more hormones. Since the claim was made (Kamm, Aldrich, Grote, Rowe & Bugbee, 1928) that the vasopressor and oxytocic principles had been separated almost completely, commercial preparations—"pitressin" and "pitocin"—have been widely used in clinical practice, the former as an intestinal stimulant and anti-diuretic, the latter as a uterine stimulant especially in the cases of pregnancy toxæmia (for which the absence of pressor and anti-diuretic properties is clearly an advantage).

Posterior lobe extracts are standardized for oxytocic activity by comparing the effect on the excised uterus of a virgin guinea-pig with that of a solution of international standard powdered pituitary, $\frac{1}{2}$ mg. of which corresponds to the oxytocic unit. One mg. of this standard preparation could be considered as containing two pressor units.

While studying the effect of drugs on isolated muscle strips taken from the human full-time pregnant uterus at caesarean section the present author, working in the Nuffield Institute for Medical Research, Oxford, observed that pitressin was a more powerful uterine stimulant than pitocin. A striking difference between the reactivity to posterior pituitary extracts of the upper and lower uterine segments was also observed.

Method. Highly purified pitressin and pitocin prepared for research purposes were used unless otherwise stated. Short strips were suspended in oxygenated Locke's solution at a temperature of 37° C. and contractions were kymographically registered. Though the form of the tracing varied, the response to a particular preparation was reasonably constant; this confirms the findings of other workers. Either an increase in tone, or an increase in the frequency or extent of the individual contractions, was judged a motor response.

All the muscle strips were from patients not yet in labour. Those from the lower uterine segment were taken from well below the attachment of the loose peritoneum; those from the upper uterine segment were taken from above that level.

When a muscle strip from the lower uterine segment and one from the upper uterine segment (both from the same human uterus) were suspended in the same bath and tested together, pitressin was about 25 times more effective than pitocin in causing contraction. The pitocin, however, contained a residual pressor content equivalent in pressor units to $\frac{1}{25}$ th of the oxytocic activity in oxytocic units; these results could therefore be explained by assuming that most, if not all, of the oxytocic activity for the isolated human uterus is associated with the pressor principle. Strips from the lower uterine segment were many times more sensitive to posterior lobe extracts than those cut from the upper segment.

When the two pituitary preparations used in these experiments were re-tested in the same apparatus, by comparing their effect on the isolated uterus of a virgin guinea-pig, the pitocin had at least 10 times the oxytocic activity of the pitressin. The fractions thus responded normally to the orthodox method of standardisation.

Summary of findings. (i) The response to pitocin and to pitressin of different muscle strips from the same part of the human uterus was reasonably constant; (ii) there was no demonstrable difference between the response of strips from the same uterus containing a preponderance of circular or of longitudinal fibres; (iii) muscle strips from the lower uterine segment were sensitive to pitressin, reacting with a motor response; in contrast, those from the upper uterine segment showed no such response to pitressin; (iv) on the isolated uterus of a virgin guinea-pig, pitocin was found to be at least 10 times more powerful as a uterine stimulant than pitressin.

Conclusions. The pituitary fraction (pitocin) chiefly responsible for the motor effect on the isolated virgin guinea-pig's uterus has a negligible effect on the isolated full-time pregnant human uterus compared with that of the fraction (pitressin) which raises the blood pressure of an anaesthetised dog.

This reversal of effect may be of the greatest importance, as extracts of the posterior lobe of the pituitary, which may be used in the induction of labour in women, are at present standardized for potency against the uterus of the virgin guinea-pig.

As the pressor, anti-diuretic, and oxytocic activities of the posterior lobe of the pituitary are present in pitressin, it may be claimed that, as far as the human subject is concerned, the evidence suggests that a separation of the pressor and anti-diuretic principles from the oxytocic principle has not been effected. Pitocin, however, has a greater oxytocic activity than pitressin on the isolated virgin guinea-pig uterus. It appears, therefore, that two powerful oxytocic principles, differing in their biological activities, have been obtained from posterior lobe extracts. Whether these two principles are similar or dissimilar in composition is a question that cannot as yet be answered. The results of these experiments demonstrate the importance of testing on the human uterus, or on the uterus of an animal which shows the same qualitative response, oxytocic substances for use in human obstetrics.

Seven kymographic tracings are reproduced in the original paper.

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352

EFFECT ON THE UTERUS OF EXTRACTS OF GORSE (*ULEX GALLII*)

by W. Smith & A. Wilson, *British Medical Journal*, 2, 322-324, 11/9/43

In parts of England an infusion of gorse (*Ulex gallii*) is a traditional remedy for retained placenta in the cow. A demonstration of its efficacy led the authors, from the Departments of Bacteriology and of Pharmacology, University of Sheffield, to test its effect on the isolated and intact uterus of certain animals, including man.

Terminal shoots of gorse from several bushes were passed through a farm hay-chopper and then through a hand tissue-grinder. Of the resultant coarse powder, 250 g. were boiled gently for half an hour in 2.5 litres of distilled water. The infusion was strained and filtered. A clear greenish-brown filtrate with a characteristic odour and acid to methyl red was obtained. Saturated solution of basic lead acetate was added until there was no further precipitation, and the precipitate was discarded. The filtrate, after removal of lead as lead sulphide, was reduced to about $\frac{1}{50}$ volume by distillation at 60-65° C. under reduced pressure. To this concentrate 9 volumes of absolute alcohol were added. A flocculent precipitate formed almost immediately, and was discarded. The alcohol was removed from the filtrate by distillation, leaving a brown viscous fluid together with gummy material adherent to the sides of the distillation flask. The gummy material dissolved readily in distilled water, and the flask washings were used to make up the total volume to exactly $\frac{1}{50}$ volume of the original infusion filtrate.

The extract obtained caused tonic contraction of the virgin and the pregnant guinea-pig uterus. The parturient guinea-pig uterus reacted with a contraction of short duration followed by prolonged abolition of uterine tone. Reactions similar to those of the isolated virgin guinea-pig uterus were obtained

from the isolated uterus of the virgin cat, the isolated uterus of the dog, and uterus of the pregnant full-term cow. The muscle strips from the upper segment of the full-term pregnant human uterus reacted with a motor response. Muscle strips from the non-pregnant human uterus reacted with a short contraction followed by inhibition of tone and sometimes relaxation.

Intra-peritoneal inoculation of 3.5 g. of the extract killed mice within a few minutes, whereas 0.35 g. and 0.7 g. caused temporary distress with laboured respiration followed by recovery. Toxic doses appeared to cause spasm of the bronchioles.

The authors discuss methods of further purification of extracts, and conclude that extracts of gorse contain a substance or substances whose dominant action is that of uterine contraction, as demonstrated on the uterus of several species including the pregnant woman near full-term.

353

A PRINCIPLE IN RASPBERRY LEAVES WHICH RELAXES UTERINE MUSCLE

by J. H. Burn & E. R. Withell, *Lancet*, 2, 1-3, 5/7/41

Infusion of dried raspberry (*Rubus idaeus*) has for long had a popular reputation as a means of facilitating childbirth. This paper, by the Professor of Pharmacology at Oxford and the Head of the Pharmacy Department of the Central Technical College, Birmingham, reports pharmacological experiments on the cat and rabbit uterus *in situ*, and on the isolated dog, cat, rabbit and guinea-pig uterus, which showed that dried raspberry leaves contain a principle (or principles) which can readily be extracted with water, and which causes:

- a. relaxation of the cat uterus when it is in tone, both *in situ* and suspended in a bath;
- b. contraction of the rabbit uterus *in situ*, and of the isolated cat, rabbit and guinea-pig uterus when these are not in tone.

Details of the experiments are given, with reproductions of 3 kymographic tracings. Observations on the effects of the infusion on intestine, spleen, and vascular system are also reported.

Pregnancy Toxæmia

354

VITAMIN B₁ AND TOXÆMIA OF PREGNANCY

by R. Kapeller-Adler & J. A. Cartwright, *Edinburgh Medical Journal*, 50, 305-314, May 1943

During recent years, some authors have claimed that vitamin B₁ deficiency is an ætiological factor in pre-eclamptic toxæmia. R. Kapeller-Adler, in whole-time service of the Medical Research Council, and J. A. Cartwright, the holder of the Vans Dunlop Research Scholarship for Obstetrics in the University of Edinburgh, 1941, report an investigation of this claim. A short summary of recent papers on vitamin B₁ in the treatment of the pregnancy toxæmias shows that there is considerable doubt as to its efficacy in hyperemesis gravidarum, neuritis of pregnancy, and pre-eclamptic toxæmia.

For the present investigation, carried out at the Royal Infirmary, Edinburgh, two groups of patients were chosen: (i) cases of mild and (ii) cases of severe toxæmia of pregnancy. The authors treated them with vitamin B₁, 25 mg. the first day and 10 mg. on the succeeding 9 days. In 4 patients with mild toxæmia there was no improvement; 3 cases of severe toxæmia became worse. Although these results were so discouraging, the investigations were continued in an attempt to determine why the vitamin B₁ therapy had not improved, and in severe cases appeared to have intensified, the signs and symptoms of the pre-eclamptic toxæmia. The authors sought a biochemical explanation and considered the possibility that histamine metabolism in pregnancy might play a significant rôle in vitamin B₁ therapy.

It has been demonstrated (Kapeller-Adler & Adler, 1943) that histidine and histamine play an important part in normal and toxæmic pregnancy. In normal pregnancy, considerable amounts of histidine and only traces of histamine are found in the urine, whereas in the toxæmias of pregnancy the

findings are different. 27 cases of hyperemesis and mild pre-eclamptic toxæmia were found to have normal or slightly diminished histidine excretion and considerable histaminuria: in contrast, in 10 cases of severe pre-eclamptic toxæmia and eclampsia, histidine and histamine were absent in the urine or were present only in traces. Kapeller-Adler suggested that histamine might be formed from the histidine present in large amounts by the activity of histidine decarboxylase. In normal pregnancy most of the histamine formed is presumably destroyed by histaminase, only traces escaping and being excreted in the urine. In milder cases of toxæmic pregnancy, e.g. in hyperemesis gravidarum and in mild pre-eclamptic toxæmia, the activity of the histaminase may be impaired and more histamine may escape and cause various kinds of intoxication; much of it, however, seems to be eliminated in the urine.

In severe cases of pre-eclamptic toxæmia and in eclampsia, a condition may arise where the activity of the histidine decarboxylase may be increased, whereas that of the histaminase may be completely inhibited. Thus most of the histidine appearing would be converted into histamine, which might then cause considerable damage to the vital organs, especially the liver and kidneys. The damaged kidneys would lose the ability to excrete histidine and histamine, which then would be completely retained in the tissues. Another possibility is that a simple failure to excrete histidine by a damaged kidney might, by exposing histidine longer than usual to the decarboxylase, cause extra histamine production and hence still more marked toxic effects. Although the presence of histidine decarboxylase in the body of pregnant women has not yet been proved, this is being investigated in the authors' laboratory. Histaminase has, however, been reported (Marcou, 1937; Werle & Effkemann, 1940; Zeller, 1941) in the serum and in the placenta of pregnant women. It has also been found that vitamin B₁ (aneurin) inhibits the activity of the enzyme. If equal quantities of aneurin and histamine are present in a solution the oxidative destruction of the latter does not take place, as the affinity of the aneurin for the histaminase is at least twice that for histamine. A further 12 cases of toxæmia were studied and it was observed that the histaminuria fell during treatment with vitamin B₁, only to rise to the previous level when treatment ceased, except in 2 cases of severe toxæmia.

The authors put forward the following explanation for the surprising fact that in the cases of mild and severe pre-eclamptic toxæmia under treatment with aneurin the histaminuria decreased. The aneurin in the circulation interferes with the action of histaminase leading to an increased blood histamine level; there results further damage to the kidney, already suffering from the increased formation of histamine characteristic of both mild and severe pre-eclamptic toxæmia, and the excretion of histamine falls. They stress the absence of evidence in the literature to support the view that vitamin B₁ deficiency does in fact exist in toxæmia of pregnancy. Taking into consideration the affinity of vitamin B₁ for histaminase, the authors believe that the therapeutic use of vitamin B₁ in toxæmia of pregnancy should be discouraged.

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355

REACTIONS TO PRESSOR SUBSTANCES IN NORMAL AND TOXÆMIC WOMEN

by F. J. Browne, *Journal of Obstetrics and Gynecology of the British Empire*, 50, 254-259, August 1943

An investigation by Schockaert & Lambillon (1937) of the effect of intravenous injection of tonaphin (an extract of the posterior pituitary lobe) showed that in (i) normal non-pregnant women, an average rise of 45 mm. Hg occurred in the systolic blood-pressure. In (ii) normal pregnant women in the last trimester the corresponding rise was 13 mm. Hg, while in (iii) patients with pre-eclamptic toxæmia it was 55 mm. Hg. General reactions differed considerably in the 3 groups. In group (i) the phenomena were very severe. Some seconds after the injection there was extreme pallor:

with cyanosed lips, accelerated respiration, dyspnoea, and an indefinable sense of malaise, followed by nausea and even vomiting, and abdominal pains, with desire to empty the bowels and pass urine. There were often cold sweats with small feeble pulse. These phenomena lasted for 7 to 8 minutes and then gradually passed away. In group (ii) general reactions might be absent or less severe, disappearing quickly—usually in 2 or 3 minutes. Shockaert & Lambillon concluded that the serum of the normal pregnant woman must contain some substance antagonistic to tonephin. In group (iii), the general reaction was less severe than in group (i), but more severe than in group (ii). It was also found that, by the 8th day of the puerperium, the rise of blood-pressure and the general reactions were similar to those obtained in group (i).

In the same year Dieckman & Michel (1937) published the results obtained by subcutaneous injection of pituitrin in 16 normal and 19 toxæmic women. In the former an average rise in the systolic pressure of 11 mm. Hg was obtained, while in the latter the average rise was 51 mm. Hg. Because of these and other findings, the authors concluded that the posterior lobe of the pituitary was concerned in the causation of toxæmia. Similar findings to those of Shockaert & Lambillon were published by de Valera & Kellar (1938).

The author of the present paper, who is Professor of Obstetrics and Gynaecology in the University of London and Director of the Obstetric Unit at *University College Hospital*, decided to repeat the experiments personally. Blood pressures were taken with subjects recumbent, and as long as possible after a meal. Estimations were repeated at more or less frequent intervals for 30–40 minutes until the base level was reached, when the pulse rate was also recorded. Tonephin (0.66 cm.³) was then slowly injected intravenously. Systolic and diastolic blood-pressure were recorded, first at intervals of about 30 seconds, and later less frequently, until the base level was reached. Throughout the experiment the objective reactions were noted, including the pulse-rate. The patients were also questioned regarding their sensations. In a proportion of all except the puerperal patients, cold pressor tests (by putting the hand and forearm in an ice bath) were also carried out for purposes of comparison. Finally, in many of the patients tonephin tests were repeated in the puerperium—in some, on two or three occasions. As the experiments have occupied the last 2½ years they extended over the worst periods of the air attacks on London, and as many of the women were evacuated to distant places in the country prolonged follow-up in the puerperium was often impossible.

The most important results may be summarized as follows:

Normal non-pregnant women. In each of 24 patients who had never been pregnant, the day of the menstrual cycle on which the test was made was noted, but this did not seem to have any constant or striking influence in the result obtained. The mean systolic rise was 21.3 mm. Hg (standard deviation, 9).

Normal pregnant women. Of 20 cases, most were at or near term and none was under 35 weeks. All were healthy before pregnancy, none had albuminuria or oedema at any time, and the highest blood-pressure reached during pregnancy had not exceeded 130/70 mm. Hg. The mean systolic rise was 33.2 mm. Hg (standard deviation, 13.3).

Pre-eclamptic toxæmia. The mean systolic rise in 20 cases during pregnancy was 54 mm. Hg (standard deviation 19.1). In many cases the rise was maintained in the puerperium.

Pregnancy with chronic hypertension. Eight tests on 7 patients in whom chronic hypertension had existed before pregnancy. The mean systolic rise was 53 mm. Hg (standard deviation, 11.4).

Normal puerperal women. Of the 20 cases none had suffered from pre-eclamptic or any other form of toxæmia during pregnancy, and the blood pressure had not, at any antenatal examination, exceeded 130/70 mm. Hg. The test was done on the 5th–17th day of the puerperium. The mean systolic rise was 48.2 mm. Hg (standard deviation, 10.75).

Discussion. These results differ materially from those obtained by Shockaert & Lambillon. One of the most striking differences is in the increases of systolic pressure in normal non-pregnant and normal pregnant women. Evidence was not found of the presence in normal pregnancy of the (anti-pressor) substance postulated by other authors. Indeed, the findings of the present author would seem to indicate that a sensitising substance may be present in normal

pregnancy. In this connection he refers to the production by Byrom (1937) of eclampsia-like lesions in rats by injection of vaso-pressin.

All investigators, including the present author, are agreed as to the great and significant increase in systolic pressure obtained in pre-eclamptic toxæmia. It is of considerable interest to note that the high reactions to tonephin in patients with pre-eclamptic toxæmia were maintained in one case up to the 235th day. The high reactions in the puerperia of women who had normal pregnancies were also very striking.

Although the mean systolic rise with tonephin was similar in pre-eclamptic patients and in those with chronic hypertension in pregnancy, the reactions to the cold test were different. In pre-eclamptic toxæmia the reaction to the cold test was low (mean systolic rise 19.2 mm. Hg) while in the chronic hypertensives it was high (46.1 mm. Hg). It is possible, therefore, that the cold test might be of value in differentiating these two conditions.

Shockaert & Lambillon emphasised the differences in the general reactions obtained in the various groups, especially in supporting their view that an inhibitory substance was present in normal pregnancy which was absent in the non-pregnant. In the present series, reactions were very variable and unpredictable, and, as the changes caused were mostly subjective, they could rarely be accurately measured. The general reaction often seemed to bear little or no relation to the amount of the rise in blood pressure.

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356

RENAL FAILURE AFTER UTERO-PLACENTAL DAMAGE

by J. Young, *British Medical Journal*, 2, 715–718, 19/12/42

In this paper from the *British Postgraduate Medical School*, the author, who is Professor of Obstetrics and Gynaecology in London University, discusses the ætiology of the shock-azotæmic state in “concealed” accidental hæmorrhage. He indicates the resemblance between this clinical state and the “crush syndrome”—a condition seen in air-raided casualties in which crushing injuries of the limbs are associated with anuria.¹ Features in common are: (i) the initial tissue damage; in one condition there is the ischæmic lesion of muscle, in the other the lesion involving a large segment of the placenta. (ii) In severe cases there is “shock,” which may be immediately fatal. In cases which survive the shock there are (iii) anuria or oliguria, and (iv) a rising blood urea followed by death or, alternatively, by an increasing diuresis and eventual recovery. (v) There is a degenerative lesion in the kidney, especially affecting the ascending limb of Henle and the second convoluted tubule, usually with the presence of pigmented blood casts in the tubules. In the crush syndrome the casts consist of myohæmoglobin, in accidental hæmorrhage (premature separation of the placenta) of hæmatin. The clinical syndrome in accidental hæmorrhage is invariably combined with the eclamptic phenomenon (pre-eclampsia and eclampsia), usually in the form of severe albuminuria, hypertension, oedema and blurring of the vision.

The present paper is based upon the study of 3 fatal cases of concealed accidental hæmorrhage and of 5 cases in which recovery followed renal impairment and azotæmia. The author discusses the ætiology under three heads:

i. **Shock.** He adduces evidence against the view that the renal failure is dependent upon circulatory collapse. In 59 consecutive cases in which severe hæmorrhage at childbirth necessitated blood transfusion, the only cases in which renal impairment developed were those with accidental hæmorrhage (5 of 10 cases). Further it could often be shown that renal failure might develop in the absence of hypotension and even in the absence of all signs of “shock.”

ii. **Hæmolysis and tubular blockage.** It had long been known that eclampsia was apt to be associated with hæmolysis and with a renal lesion associated with tubular degeneration and with hæmatin casts in the tubules (Schmorl, 1893;

¹ [see *BMB* 3 for a bibliography on this syndrome.]

Brütt & Schumm, 1918 ; Fahr, 1924 ; Seitz, 1927 ; Dunn & Baird, 1933). In the crush syndrome, as Bywaters & Beall (1941) showed, the urine may differ little from a glomerular filtrate. This indicated severe damage even in non-obstructed tubules and was against the view that the renal failure was entirely explained by tubular obstruction. Further, in both the crush and accidental hæmorrhage states there might be tubular degeneration in the absence of casts (e.g., in an early case).

iii. *Toxic agent of tissue origin.* The present author has indicated elsewhere (Young, 1942) that the elimination of competing ætiological factors served to direct attention to the immediate influence of the massive placental damage. It was well known that albuminuric toxæmia and renal failure were more frequent in the "concealed" than in the "revealed" type of accidental hæmorrhage. Young, in previous communications (1914 ; 1927 ; 1942), discussed the significance of "concealment" in accidental hæmorrhage. A distinctive feature was that in this condition the damaged placenta was "concealed" within the uterus and that where the circulation was maintained in the undamaged part, with resulting foetal survival, the conditions were such as to favour the escape into the systemic blood stream of any toxic materials generated in the dying area. Young (1942) also showed that there was a quantitative relation between (a) the severity of the toxæmia, and (b) the mass of the placenta involved and the period of foetal survival. This evidence formed the basis of the placental hypothesis of the eclamptic phenomenon (Young, 1914 *et seq.*).

The author has also presented evidence (Young, 1927 ; 1942) that accidental (retroplacental) hæmorrhage is an expression of, and is determined by, an antecedent "abortion taint," which is usually hormonal in origin. In 20 cases of "concealed" accidental hæmorrhage, he found azotæmia in 5, or 25 per cent. Azotæmia was rare in pre-eclampsia.

From the foregoing clinico-pathological study of the syndrome in concealed accidental hæmorrhage it is suggested that (i) the syndrome is determined by a massive utero-placental lesion of ischæmic origin, (ii) the renal failure characterized by tubular degeneration and azotaemia is determined by a toxic material derived from tissue autolysis, (iii) the shock element and the hæmolysis which are often present may have a similar origin.

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357

THE PLACENTA IN ECLAMPSIA AND NEPHRITIC TOXÆMIA

by N. M. Falkiner & J. O. E. Apthorp, *Journal of Obstetrics and Gynecology of the British Empire*, 51, 30-37, February 1944

This paper is based on a study of over 100 toxæmic cases occurring in the Rotunda Hospital, Dublin. The authors, who are the Master and Assistant to the Master in the Hospital, have examined placenta and have described three stages of infarction. First stage, extreme injection of large and small vessels in the villous tree, extending to the terminal capillaries and associated with narrowing of the intervillous spaces. Second stage, obliteration of the intervillous spaces with commencing loss of structure. Foetal blood is still seen. Third stage, the whole infarcted area is becoming homogeneous in appearance. They claim that the acute placental lesion is associated with eclampsia and the chronic lesion with nephritic toxæmia, and describe in detail nine case histories ; photographs, with explanatory diagrams, of the cut surfaces of 9 placenta are included. [Criteria for the diagnosis of nephritic toxæmia are not given.]

Conception and Development

358

DISCUSSION ON NEW DEVELOPMENTS IN THE INVESTIGATION AND TREATMENT OF STERILITY by V. B. Green-Armytage, K. Walker, E. W. Wittkower (and others), *Proceedings of the Royal Society of Medicine*, 36, 105-112, January 1943

Childless marriages are not infrequently unhappy partnerships. Any new developments, therefore, in the investigation and treatment of sterility are of especial importance both to the individual and to the community as a whole.

At a meeting of the Section of Obstetrics and Gynecology of the *Royal Society of Medicine*, the discussion was opened by the Gynecologist to the West London Hospital, the late Professor of Obstetrics, Gynecology and Surgery at the University of Calcutta. The importance of uterine and endocrine development, and/or the condition of the cervix, in cases of primary infertility were compared with the relatively rare finding of tubal occlusion. The speaker described two groups each of twenty healthy young married women observed over a period of two years. Those in Group 1 were persuaded to live an absolutely normal sex life, while those in Group 2 had from the beginning of married life made use of chemical douches or occlusive caps with medicated pessaries, or they stated that their husbands used condoms or adopted *coitus interruptus*. It was observed in the group of women leading a normal sex life, that five cases in whom the uterus was normal in size and shape, rapidly conceived. In fifteen the uterus and ovaries were palpably small and immature ; of these, nine grew to normal size in 4½ to 6 months and conception occurred after an average of 7½ months of married life. Those women (Group 2) practising some form of contraception were examined after a period of one to two years. In ten cases the uterus was palpably small and hypoplastic and in five there was a small annular erosion around the external os.

These observations suggested that human semen contained a substance which, absorbed from the vagina, might assist the full development of the female genitalia. Animal experiments were therefore carried out in the *Pearson Foundation Research Laboratory* under the direction of Professor Silberstein at the West London Hospital. The preliminary results showed that the intramuscular injection of human semen into immature ovariectomized female rats caused hypertrophy of the uterus. It was suggested that the substance responsible for this effect is probably testosterone or a hormone allied to it, as was suggested by Noble (1939). Further experiments are required before it can be stated whether or not the action of this hormone is local, or central through an action on pituitary secretion.

The conclusion was reached that "anything or any method which prevents, retards, or alters the normal degree of physiological absorption of human semen from the vagina, carries with it during the early months and years of marriage the risk of future sterility." The importance of a viscid, opaque, yellow, infected cervical mucus plug as a cause of sterility was also stressed.

The second speaker, who is Surgeon in charge of the genito-urinary department of the *Royal Northern Hospital*, London, discussed the importance of the male in sterility, and referred to the method of testicular biopsy, which he and his co-workers first used to differentiate between cases of azoospermia due to a blockage in the ducts and those resulting from aspermatogenesis. More recently this diagnostic procedure had been extended to other types of infertility. Three groups of abnormalities in the seminiferous tubules may be distinguished. (i) A limitation in the intensity of epithelial activity which sometimes extends to the reduction of the epithelium to a single layer of indifferent cells. (ii) Maintenance of epithelial activity with incomplete differentiation. For instance, spermatocytes may be present in large numbers but may fail to change into spermatids. (iii) The existence of a differentiation which is faulty. Out of 77 husbands examined, fertility was satisfactory in 23.4 %, doubtful in 37.6 %, markedly impaired in 18.2 %, and in 20.8 % there was complete sterility.

The third speaker described the results of a psychological investigation of sterility, and the characteristics of a personality type prevailing among sterile women. The vast majority of such patients were diffident in manner, juvenile, or younger

than their years in appearance, and without marked secondary sexual characteristics. They were often more ambitiously dressed than others of their class, or so differently, especially in relation to their use of make-up, that their total appearance could be best described as doll-like. Individuals of this type had frequently been the youngest or only children, obviously over-attached to the family rather than to either parent. Intensely shy, especially with adults, they disliked school because of the roughness of other children and preferred to stay at home, even in adolescence. Many of them as adults are interested to an unusual degree in their personal appearance, and obviously desire to attract, but neither before nor after marriage have they ever experienced any genuine adult sexual feeling. In fact, they are almost completely frigid and, corresponding to this, incapable of any deep affection. A small sub-group of patients complaining of sterility are obese women with strongly marked maternal attitudes. The speaker concluded that in a holistic approach to the problem of sterility a certain significance must be attached to mental factors.

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[*Sterility and Impaired Fertility: Pathogenesis, Diagnosis and Treatment*, by C. Lane-Roberts, A. Sharman, K. Walker & B. P. Wiesner (Hamish Hamilton Medical Books, London), is a comprehensive and authoritative modern work on this subject.]

359

SOME RECENT STUDIES AND INVESTIGATIONS IN STERILITY

by A. Sharman, *Proceedings of the Royal Society of Medicine*, 37, 67-72, December 1943

In this paper the author reports investigations on various aspects of sterility in women, based on a series of 500 consecutive unselected cases, with additional cases selected for special reasons. A more detailed account of these investigations has since been published (Sharman, 1944).

Estimation of Patency of Fallopian Tubes

A total of 1003 insufflations was performed in 480 cases. In many cases simultaneous kymographic tracings were made. In some cases in which insufflation appeared to demonstrate non-patency, the later occurrence of pregnancy, or a subsequent kymographic tracing characteristic of patency, demonstrated that single tests were unreliable. In 2 such cases patency was demonstrated only by insufflation under anaesthesia. The author dismisses the view that a positive second test is due to the therapeutic effect of the first test, on the ground that subsequent insufflations in cases in which there have been 2 or more previous tests were without effect. Other possible causes of reversal of negative first tests were investigated, and the author concludes that neither anaesthesia, nor relation of time of insufflation to phase of the menstrual cycle, nor rate of flow of gas were responsible.

Hysterosalpingography was performed in a number of cases for purposes of comparison. There was, in general, good correlation of results. In insufflation, the source of error is reliance placed upon a single test. In hysterosalpingography it is in the interpretation of the radiographs.

ii. Anovular Menstruation as Assessed by Endometrial Biopsy

In 358 cases in which biopsy was performed in the premenstrual phase, the endometrium showed the normal features in 335. In the remaining 23 cases, biopsy indicated anovulatory cycles, which the author differentiates as (a) "periodically anovular" and (b) "constantly anovular." None of these 23 patients became pregnant during the period of observation, but pregnancy followed treatment in 2 of them. The author concludes that non-ovulation is an important cause of sterility, although its incidence is low.

iii. Endometrial Tuberculosis

Endometrial biopsy in 392 cases showed unsuspected tuberculosis in 20. In a later series of 448 consecutive cases, examination of the endometrium revealed tuberculosis in 22. There was therefore tuberculosis in 5% of 840 cases. The characters of endometrial tuberculosis have been discussed in detail by Sutherland (1943), and from his further observa-

tions it appears that this condition is 15 times more common in sterile than in fertile women. A negative biopsy does not exclude endometrial tuberculosis, and its actual incidence in sterile women is probably higher than 5%. In 6 patients who were examined over a long period, endometrial tuberculosis was still present after 2½-7½ years. No patient with endometrial tuberculosis became pregnant. In 4 patients on whom thorough curettage was performed, tuberculous endometrial infection rapidly recurred. In most cases, a history or evidence of previous tuberculosis was obtained.

In 35 cases of endometrial tuberculosis in which insufflation was performed, there was occlusion of the fallopian tubes in 29 (83%).

iv. Causation of Tubal Occlusion

There is little evidence that *gonococcal salpingitis* is a common cause of tubal occlusion, except in cases in which the tubes are palpably thickened.

On the evidence of (a) histological studies of the prepubertal tube, (b) insufflation of the tubes in the foetus and infant, (c) kymographic insufflation in unselected consecutive series of unmarried women, the author concludes that *congenital hypoplasia* of the tubes is seldom a cause of impermeability.

In view of the relatively high incidence of endometrial tuberculosis in sterile women, the high incidence of tubal occlusion in patients with endometrial tuberculosis, and the known fact that gross infection of the tubes may be present without endometrial involvement, the author suggests that occlusion due to *subclinical tuberculous salpingitis* may be a cause of sterility in a considerable number of cases.

Sections of fallopian tube removed in the course of salpingostomy from 3 women who consented to the operation all showed evidence of tuberculosis infection on histological examination.

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360

INTELLIGENCE AND SEASON OF CONCEPTION

by J. A. F. Roberts, *British Medical Journal*, 1, 320-322, 4/3/44

There is substantial evidence of a tendency for children conceived in winter months to be more intelligent than those conceived in summer. It has been generally assumed that the explanation lies in an influence of the season upon intelligence, and Mills (1941) and other writers have suggested that prospective parents should for this reason plan for winter conception.

The author, who is director of the Burden Mental Research Department of Stoke Park Colony, Bristol, has examined this question on the basis of data obtained from a representative sample of 3361 schoolchildren. It was confirmed that winter-conceived children were, on the average, of slightly greater intelligence than summer-conceived children. However, when winter-conceived children were compared with their summer-conceived brothers and sisters, the difference vanished.

The conclusion of this study is that intelligence (parental) influences season of conception, or, in the author's words, that there is "a tendency for the children of more intelligent parents to be conceived slightly more often in winter, those of less intelligent parents slightly more often in summer."

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361

PHASES OF MATURATION, FERTILIZATION AND EARLY DEVELOPMENT IN MAN

by W. J. Hamilton, J. Barnes & G. Dodds, *Journal of Obstetrics and Gynaecology of the British Empire*, 50, 241-245, August 1943

In this paper, from the Anatomy Department, St. Bartholomew's Hospital, London, and the Obstetric Unit, University College Hospital, London, the authors describe an unfertilised human ovum showing the second maturation spindle,

an unsegmented ovum at an early stage of fertilisation, and a young chorionic vesicle partially implanted in the endometrium.

The first specimen was recovered at operation by flushing the uterine tube on the 17th day of the menstrual cycle; ovulation had probably occurred less than 12 hours before. The previous cycle was of 30 days' duration. In the fresh state, the ovum was surrounded by several layers of *corona radiata* cells which were attached to a homogeneous *zona pellucida*. The *vitellus* was yellowish in colour, uniformly finely granular, and completely filled the zonal cavity. It did not show the three types of yolk bodies described by Lewis (1931), but resembled more closely the second ovum described by Pincus & Saunders (1937).

After fixation and section the ovum was found to be at the stage of the second maturation spindle. The polar body showed scattered chromosomes in its cytoplasm. The appearances in this specimen do not support Dixon's (1927) opinion that the second maturation spindle is completed before ovulation.

The second specimen was recovered on the 16th day of the cycle from a woman who had previously had a 28-day cycle. Coitus had taken place 2 and 4 days previously. In the fresh state, the ovum was free of *corona radiata* cells. The *zona pellucida* appeared as a homogeneous membrane in which many completed spermatozoa were found. The *vitellus*, which did not completely fill the zonal cavity, showed a clearer zone in the centre; its general appearance was that of early degeneration. At one side there were a number of granules, probably remains of the polar bodies.

The third specimen (the "Barnes" embryo), an early chorionic vesicle partially implanted in the endometrium, was found on the 25th day of the menstrual cycle. The endometrium in the cervix and in the lower body was hypertrophic and polypoidal. Elsewhere it appeared to be normal. An elevation was just visible in approximately the middle of the posterior wall. With a low power binocular microscope, it appeared as a slightly raised translucent area clearly demarcated from the surrounding endometrium; it was tentatively diagnosed as a young implanting blastocyst or a retention cyst of a uterine gland.

Microscopical examination of the sections showed an early implanted blastocyst. The chorionic vesicle is not completely implanted in the endometrium, as part of the elevation that projects into the uterine lumen is not yet covered by the uterine epithelium. The trophoblastic shell is thickest over the deep embryonic region of the vesicle and thinnest in the abembryonic region where the uterine epithelium is absent; it is differentiated into a cytotrophoblast and a syncytiotrophoblast. The calculated dimensions of the vesicle are approximately $0.931 \times 0.770 \times 0.737$ mm. In some areas the syncytiotrophoblast had destroyed the walls of the blood vessels, allowing the blood to escape to a slight extent. The general appearances closely resembled those described by Hertig & Rock (1941). The cytotrophoblast is composed of cuboidal cells which, in some situations, have proliferated to form irregular masses which project into the syncytiotrophoblast; these projections are the fore-runners of the primary villi.

The endometrial tissue shows marked oedema, but there is no evidence of a decidual reaction. The epithelium seems to be resistant, at this stage, to the action of the syncytiotrophoblast and the dilated and tortuous glands appear to be pressed aside by the expanding vesicle.

The embryonic disc is convex towards the amniotic cavity and is composed of tall columnar epithelial cells which are continuous at the periphery of the disc with the amniotic ectoderm. This for the most part consists of a layer of flattened cells, but in one situation these cells are cuboidal. The endoderm is composed of from one to several layers of large cuboidal cells with vacuoles in their cytoplasm. An endodermal yolk sac has not yet been formed, but a cavity lined with endodermal cells and flattened mesodermal cells (Heuser's, or exocoelomic, membrane) encloses a cavity which has been designated by Hertig & Rock in their specimens as the exocoelomic space. In this cavity there is a precipitated coagulum. The outer aspect of the cells of Heuser's membrane is continuous with a mesenchymal reticulum which fills the trophoblastic vesicle except where it has become artificially separated from the cytotrophoblast. The age of the embryo is estimated to be from 10 to 11 days.

The paper is illustrated by 7 photomicrographs.

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362

A STUDY OF CRANIOLACUNIA

by J. B. Hartley & C. W. F. Burnett, *Journal of Obstetrics and Gynaecology of the British Empire*, 50, 1-12, February 1943

Cranio-lacunia is the name recently suggested to replace the term *Liickenschädel*, hitherto used to describe a curious and striking appearance in the bones of the skull in infancy. The authors, who are Consultant Radiologist to the *Christie Hospital and Holt Radium Institute*, Manchester, and Resident Obstetrical Officer to the *Stepping Hill Hospital*, Stockport, support the use of this new name because it describes more accurately the appearances upon which the diagnosis depends; moreover the word is in accord with the approved terminology of similar conditions, for example, craniostenosis.

Cranio-lacunia is characterised by an abnormal development of the bones of the vault of the skull, in which thick bony bars or ridges are formed on the inner surface of both squamous temporal, parietal, and frontal bones, and the squamous occipital. These bars run a variable course from case to case, sometimes diverging and then converging, forming a network so as to enclose between them lake-like areas, where ossification is diminished or absent and where the thickness of the bone is correspondingly reduced. Sometimes the bars are broad and dense, with the lacunæ poorly defined or shallow: in other cases (as in hydrocephalic skulls), the lacunæ are large, very numerous, and relatively deep, the bars being of varying thickness. The outer surface of the bones is smooth. The lacunar appearance is seen *in vivo* only by radiography. After death it may be seen by radiography, trans-illumination, and direct inspection. The condition may be so marked as to allow confident radiological diagnosis at the 7th month of foetal life, or so slight as to be dubious on good x-ray films taken in early infancy.

The authors describe eleven new cases. They emphasise that the condition is relatively common, appearing in about 1% of all births. They discuss various aetiological theories, and point out that the evidence presented does not support Engstler's (1905) proposition that the developmental defect is due to the diminution of blood supply resulting from occlusion of the vertebral arteries. They could find no evidence that this occurs: moreover, it would not explain the frequently associated spinal defect. Cohn (1924), who first reported the existence of cranio-lacunia in normal infants, maintained that it was merely a manifestation of delayed development in such cases; Vogt & Wyatt (1941) also reported two similar cases. The present authors agree that the condition does exist in otherwise normal infants (as in one of their own cases), but it cannot be an expression of delayed development because the bars and ridges of a cranio-lacunar skull in a foetus of 8 months were thicker than the bones of the normal skull at term. It is thus a disorder of development and not a simple under-development.

All observers have stressed the frequent association of cranio-lacunia with other developmental defects such as talipes and spina bifida; the latter may be either myelocoele or meningocele, single or multiple, small or large, and may occur in any region of the spine. Encephalocele is also described.

Doub & Danzer (1934) alone have recorded the presence of deformed ribs in a single instance. All these types of defect have occurred in the present series. No evidence was found to suggest that any recognised disease plays a part in the causation of cranio-lacunia.

The most popular explanations of the lacunar changes in the vault bones of the skull are those based upon supposition of abnormal pressure bearing upon the developing skull, either from without or from within. Kassowitz, who suggested the theory of external pressure, considered that it was exerted on the skull during labour and was sufficient to account for the changes observed. Although finding no supporters, his suggestion was never rejected, because the diagnosis of cranio-lacunia prior to delivery had never been made. The present series finally disposes of this theory, since the definite antenatal diagnosis was made in two cases

4 weeks and 3 weeks respectively before the calculated date of delivery. The theory of increased pressure upon the bones from within, by means of increased intracranial pressure, was accepted by many authors, from von Recklinghausen in 1886 to Shearer in 1937, and was based on the assumption that the lacunæ corresponded to and were produced by the cerebral convolutions. However, in 1941 Vogt & Wyatt doubted whether the developing infantile brain, which is gelatinous in consistence at this age, could cause convolutional impressions in the skull bones. The present authors claim to have completely disproved this internal pressure theory because, in one case at necropsy, it could be seen that the gyri did not fit into the lacunæ; the bony bars were crossed at all angles by the convolutions and the two patterns were entirely dissociated.

In one case the craniolacunias was of a more pronounced character than in the others. There were complete defects of ossification, actual perforations being more frequent than lacunæ. For this exaggerated form of the condition, the authors feel that a separate name should be applied; they suggest the term *craniofenestria*.

In summarising their findings, the writers claim that the material already observed has been sufficient to eliminate most of the theories previously suggested to explain this condition. In their opinion craniolacunias is a defect in which two processes are frequently associated; the faulty ossification of the primitive membranous vault which surrounds the early brain, and the faulty chondrification of the vertebral bow of the primitive membranous spinal column which surrounds the early spinal cord. As with so many congenital abnormalities, the cause is at present obscure.

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3

NEW LIGHT ON THE ORIGIN OF CRANIOLACUNIA

J. B. Hartley & C. W. F. Burnett, *British Journal of radiology*, 17, 110-114, April 1944

In a previous paper the authors (Hartley & Burnett, 1943) presented evidence against some of the theories on the origin of craniolacunias, leaving open the possibility that the condition might result from (a) a chromosomal developmental defect, or (b) a dietetic, vitamin or hormonal deficiency.

In the present paper they report a case of circumscribed craniolacunias which throws some light on the aetiology of the condition. A woman of 38 was delivered of a stillborn foetus. Gross hydrocephalus had been detected before labour, and 30 ounces [about 850 cm.³] of cerebrospinal fluid had been withdrawn by paracentesis of the foetal head. In spite of this measure, there was still considerable hydrocephalus at birth. Examination of the skull bones showed the following abnormalities:

- i. *Frontal bones.* Marked lacunæ anteriorly and centrally; little change peripherally and posteriorly.
- ii. *Parietal bones.* Little change.
- iii. *Occipital bone.* Much expanded distal portion of squamous occipital bone derived from membrane; stunted growth and variable density of proximal segment derived from cartilage.

These appearances suggest that the cause of the condition was operative only during the early months of ossification, and diminished in effect as the pregnancy proceeded. Intracranial pressure could not produce such localised changes. The fact that craniolacunias diminishes (and probably disappears) in surviving cases is against a developmental defect.

The authors conclude that the most probable explanation of the cause of the condition is a nutritional defect in early pregnancy.

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¹ [see BMB 362]

Nutrition: Lactation

364

THE DIETARY FACTOR IN REPRODUCTION AND LACTATION

by M. B. Richards, *British Medical Journal*, 2, 418-419, 2/10/43

The author, writing from the Rowett Research Institute, Aberdeen, points out that it is difficult to assess the importance of nutrition in infant welfare because there are a number of uncontrollable factors other than food which affect the health of infants. Using small animals, however, it is possible to control the environment and thus obtain more accurate figures on the specific effect of a deficient dietary on the mortality of young animals.

The experiments described in this paper are designed to determine the effect on reproduction in rats, of supplementing a poor human dietary (used as their basal diet) by additions of inorganic calcium and vitamin B₁, given separately and in conjunction; to test the effect of dried yeast as a source of vitamin B₁ and other factors; and, further, to test the influence during the breeding period of an increased milk intake in addition to these supplements.

The basal diet employed was the same as that described by Richards (1943), and represents the average diet of households spending from 3 to 7 shillings a head weekly on food.

The addition of extra milk to the diet was beneficial. The weights of the young at weaning and of the mothers after weaning were greater than those of animals not receiving milk, and there were also more young born alive per litter and a greater proportion of litters of eight were reared.

The addition of calcium alone to the basal diet increased the number of live young per litter and raised the proportion of litters of 8 reared. These increases were no better than those brought about by milk. The calcium also increased the weaning-weight of the young, but not as much as milk. The addition of vitamin B₁ alone was of doubtful value.

The addition of calcium and vitamin B₁ reduced the percentage of stillborn and increased both the weaning-weight of the young and the weights of the does after lactation.

The addition of calcium and yeast to the basal diet produced outstanding results. The number of live young per litter and the proportion of litters of 8 reared were greatly increased. There was also a considerable improvement in the weaning-weight. This was increased still more by adding milk to the yeast and calcium.

The results of these experiments indicate that the yeast supplement corrected certain deficiencies in the diet which were not corrected by supplying calcium, milk and vitamin B₁. They show clearly the importance of the diet in matters concerning breeding performances in animals in controlled environment, and indicate the large part that it may possibly play in the problem of infant mortality in human beings.

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365

FAILING LACTATION

by M. Robinson, *Lancet*, 1, 66-68, 16/1/43

In this paper the author reviews the physiology of lactation and reports observations made on a large series of mothers in which there was a failure to continue breast-feeding. The normal filling of the breasts is associated with a gradual increase in the sense of heaviness lasting about 30 minutes and ending in a sudden tightness, possibly due to fluid. They are emptied in about seven minutes by a rhythmic pumping out of the milk at the rate of 60 jets per minute. Pumping occurs spontaneously when the breasts are allowed to get over-full or when the other breast is stimulated. If the smooth muscle found by Swanson & Turner (1941) in animals is present in women, the pumping may be initiated by the posterior pituitary gland (Schäfer, 1913). For 2½ to 3 hours after emptying, the breasts excrete no milk in quantity. Schäfer's work (1914-15) confirms this.

Lactation may not commence at all, or may fail to be adequate, or may dry up completely at any time during the nine months of lactation. The amount of breast tissue

present varies from woman to woman (Engel, 1941), possibly due to deficient secretion of mammogen I and II during pregnancy (Mixner, Lewis & Turner, 1940). The gradual premature failure of lactation is not a uniform lowering of the normal rate of secretion (Tallerman & Hamilton, 1928) but is a lengthening of the interval between each filling of the breast, as well as a reduction in the amount of milk secreted at each filling. The condition is aggravated by muscular exercise, emotion and loss of sleep, and is not prevented by regular suckling.

Other women, during the first four months of lactation, fail through a continuous lactorrhœa which prevents the breasts retaining the milk owing to over-activity of the pumping mechanism; while yet others fail because the breasts, during the first six weeks, become over-full of solid matter owing to paralysis of the pumping mechanism.

In 1,100 failures investigated by the present author, no cause could be found in 438, and the failures included all four types of lactators as defined by Robinson (1942). The health of the mother (255), the condition of the infant (136), and the environment (91) were the reasons given for weaning. By 33 of the mothers the fault was attributed to the breast, and by 103 to the nipples. Neither menstruation nor a superimposed pregnancy affected the milk secretion. Acute illness caused a temporary failure in 48 mothers, and a complete failure in 59. Prematurity (12), twins (22), and deformities of the infant (7) were associated with a poor milk supply.

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¹ [typewritten abstract available on request]

366

A REFLEX GOVERNING THE OUTFLOW OF MILK FROM THE BREAST

by H. K. Waller, *Lancet*, 1, 69-72, 16/1/43

The author discusses two aspects of lactation :

i. *The failure of milk secretion in the early weeks.* A close association is claimed between early failure and the overloaded state of the breasts which commonly follows the start of active secretion. In a series of 52 women, 34 suffered from engorgement in the puerperium, and the infants of 24 of these were being bottle-fed before the end of the first month. With engorgement the outflow of milk is much impeded and may be completely obstructed. The author attributes this to lymphatic œdema affecting all the mammary tissues including the ducts. The nipple is liable to damage for the same reason, and this occurred in 30 cases in the present series, with 3 cases of mastitis. Unless rapidly relieved, overloading leads to suppression of secretion by compression of the secretory cells and interference with their nutrition.

ii. *A reflex expelling mechanism.* This moves the milk forward from the recesses of the gland to the larger ducts and sinuses, whence it may be ejected beyond the nipple. The reflex is accompanied by a tingling sensation in the breasts known as the "draught," and it seems to be identical with the rise of pressure responsible for "letting down" the milk in animals, shown by Tgetgel (1916) to be over 20 mm. Hg. The rise is sudden and of short duration. In Hammond's (1936) view it dislodges the fat-laden fraction of milk from the alveoli and smallest ducts, where it is retained by capillary attraction, into the larger tubules and reservoirs. This explains the difference in fat content of fore and hind milk. In the cow this difference is most marked in milk withdrawn from the first quarter of the udder milked. By the time the fourth quarter is milked, the fat has been diffused and the difference is almost obliterated. The fat content of fore and hind milk expressed at the appropriate moment from the human breasts shows the same difference. The author gives the average figures of samples from 14 women :

		Fat content	
		1st breast	2nd breast
Fore milk	- - -	3.4 %	4.9 %
Hind milk	- - -	7.6 %	6.8 %
Rise	- - -	4.2 %	1.9 %

The milk was withdrawn manually by a technique described in the original paper.

The author discusses the significance of the "draught" reflex, its liability to disturbance and inhibition, and its conditioning as lactation proceeds. It is not as a rule felt early in the first lactation, and it is suggested that this is due to overloading of the breasts. The continuance of secretion depends on effective emptying, and the "draught" is the means by which this is contrived. The child's suction draws the nipple into the position in which milk can be squeezed from the sinuses by the action of the mandible. In the author's opinion, conditions favouring reflex emptying would repay study; current rules for feeding may not correspond with physiological needs. The figures given are against the practice of putting the child to one breast only, in order that it should obtain milk of high fat content. This favours overloading and involves risk of suppressing secretion.

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Plastic Surgery

367

A UNIQUE CONSTRUCTIVE OPERATION

by V. Bonney & A. H. McIndoe, *Journal of Obstetrics and Gynaecology of the British Empire*, 51, 24-29, February 1944

This paper, written jointly by a gynaecologist and a plastic surgeon, records an operation performed upon a girl of 18 with congenital absence of the vagina and a double uterus. It was decided that an artificial vagina should be made by McIndoe's (1938) technique, using a split-skin graft taken from the inner aspect of one thigh, and that the two uterine bodies should be joined and a cervix constructed.

At operation it was found that (i) no cervixes were present; (ii) the uterine bodies were very laterally placed and (a) terminated in a sheet of tissue about ¼ inch [6 mm.] thick which appeared to pass into the cardinal ligament on each side, (b) lay about 2½ inches [6.3 cm.] above the track made for the new vagina.

On opening the uteri, it was found that they contained only a slight amount of menstrual blood. The sheet of tissue in which the uteri terminated was then divided mesially as far down as the vaginal track, which was thus placed in communication with the abdominal cavity. The cut inner aspects of the uteri were then trimmed and the posterior edges were sutured together. The sutures were continued downwards to unite the divided sheet of tissue in which the uteri terminated. A piece of tube, with a small split-skin graft adhering to a segment of it, was passed from above into the vaginal track. Its upper extremity lay in the common cavity of the posteriorly joined uteri, the middle skin-covered segment at the site planned for the artificial cervix, and the lower end in the vaginal track. The twin uteri were then sutured anteriorly, enclosing the tube, and a cervix was constructed around the skin-covered segment of the tube from the divided sheet of tissue in which the uteri had terminated. The vaginal track was then lined by a split-skin graft applied to a mould (containing an aperture through which the tube passed).

The end results of the operation were remarkable. The first definite menstruation occurred 109 days after the operation, and after two further menstrual bleedings at irregular intervals, the patient started to menstruate regularly every 28 days, and has continued to do so (at the time of writing, 14 months after operation). Menstruation lasts 2-3 days and bleeding is moderate.

REFERENCE

McIndoe, A. H. (1938) *J. Obstet. Gynec.* 46, 490

ENDOCRINE THERAPY IN GYNÆCOLOGY AND OBSTETRICS

by P. M. F. Bishop, *Journal of Obstetrics and Gynæcology of the British Empire*, 51, 51-63, February 1944

This is a critical review, principally based on work reported during 1938-1943, by the Clinical Endocrinologist to Guy's Hospital, London. The author summarises the advantages and disadvantages of oral administration of synthetic œstrogens, refers to new routes of administration such as the sublingual and the subcutaneous implantation methods, and discusses the scope of œstrogen therapy. The use of progesterone or androgens in abnormal uterine hæmorrhage, of progesterone in threatened and recurrent abortion, of various sex steroids in dysmenorrhœa, and of gonadotrophins in ovarian deficiencies is also reviewed.

THE NOMENCLATURE OF HORMONE-PRODUCING TUMOURS OF THE OVARY

by H. Burrows, *Journal of Obstetrics and Gynæcology of the British Empire*, 50, 430-432, December 1943

Increasing knowledge of gonadal hormones and ovarian tumours has demonstrated that some of the terms applied to the latter are misleading. The writer, from the Chester

Beatty Research Institute, Royal Cancer Hospital, criticises two such terms, *arrhenoblastoma* and *granulosa-cell tumour*, both terms applied to ovarian tumours which determine the manifestations of sex.

Arrhenoblastoma means strictly a tumour arising from a masculine rudiment. Two reforms are suggested to permit the terminology to accord with fact; the first is to shorten the term to *arrhenoma*, which means "male tumour" and makes no assumption as to its origin in a testicular vestige; the second is to apply the term *arrhenoblastoma* to all tumours, whether situated in the ovary, adrenal or elsewhere, which produce excessive amounts of androgen and so bring about virilism.

Granulosa-cell tumour. Strictly the term is applied to ovarian tumours the cytology of which recalls the granulosa tissue of ripening follicles and the effects of which are those produced by œstrogen. In practice œstrogen-producing tumours of the ovary whose cytology would not support the title, have been called granulosa-cell tumours. If, as some believe, these tumours do not arise from the granulosa tissue of ripening ovarian follicles, the term is misleading. It is still unproven that the granulosa-cells of normal ovarian follicles form œstrogen, and not every tumour having the appearance of granulosa tissue will cause œstrogenic effects. Ovarian tumours composed of cells which do not resemble those of granulosa tissue may yet supply an excess of œstrogen. The writer therefore suggests the term *theeloma* to denote those tumours which produce œstrogen, irrespective of their location in the body, or of their histological appearance.

BOOKS, MEMORANDA, REPORTS

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CAESAREAN SECTION

The History and Development of the Operation from Earliest Times

J. H. Young. London, H. K. Lewis & Co., 1944. 254 pages. 1s. [£0.8]

The author divides the history of the caesarean operation into three periods—before 1500, between 1500 and the development of modern technique of the operation by Porro in 1876, and after 1876. The third period includes the work of Max Sänger, the revival of the lower segment operation by Gaillard Thomas and Fritz Frank, and the introduction of the Portes operation. This book is the result of a careful study of the literature dealing both with the nomenclature and the operative technique of caesarean section, one of the oldest operations in the history of medicine. The author discusses the origin of the term and presents evidence refuting the general belief that the operation was used during the birth of Julius Cæsar and that it was named after him. An account is given of the earliest reported cases, and their authenticity is carefully examined in the light of modern obstetric knowledge. Each advance in the technique of caesarean section is traced in detail, from the crude operation practised in former times as a last-minute attempt to extract a living child from an almost moribund mother, to the carefully planned operation of to-day with its advantages of modern methods of asepsis and anaesthesia. This exhaustive study of the subject includes liberal extracts from many of the important writings on the caesarean operation. Ample bibliographies in each chapter are evidence of the thoroughness with which the writer has pursued his subject. The book concludes with an examination of the medico-legal aspects of caesarean section and of sterilization performed during the operation. Adequate indexes, both of personal names and of subjects, are provided.

A TEXTBOOK OF PATHOLOGY General and Special

by J. M. Beattie & W. E. C. Dickson, with the collaboration of A. M. Drennan and J. O. Oliver. 4th edition. London, W. Heinemann (Medical Books), 1943. 1,368 pages; 828 illustrations. £4 4s. [£4.2]

The task of bringing up to date such a large work as this, especially during wartime, must have been considerable. The book last appeared in 1926 and in this fourth edition some new subjects have

been introduced—virus diseases, disorders of the female reproductive organs, and the avitaminoses. The remainder has been carefully revised; particular attention has been paid to the chapters on blood diseases and on the nervous system, and the latter is especially to be commended. Modern pathology has not been overlooked, and the reader will find information on such subjects as blast injury and injuries incidental to flying; the classification of the reticuloses is included. Bacteriology is excluded, but a section is devoted to animal parasites.

The book includes a large number of illustrations, many in colour, and all of a high standard; copious references for further reading are given. A particularly satisfactory feature is the very detailed index, which occupies 100 pages and has the main headings in heavy type.

THE VASCULAR ABNORMALITIES AND TUMOURS OF THE SPINAL CORD AND ITS MEMBRANES

by R. Wyburn-Mason. London, H. Kimpton, 1943. 196 pages; 42 illustrations. 18s. [£0.9]

The work of Lindau, Cushing, Bailey, Dandy, Olivecrona and others has drawn the attention of neurologists to the vascular anomalies and tumours of the forebrain, but hitherto no attempt has been made to systematize the knowledge of such conditions as they affect the spinal cord and its meninges. In this book the author has drawn attention to the relative frequency of vascular abnormalities and neoplasms in the spinal cord and has attempted to correlate clinical and pathological findings, thus providing a basis for accurate diagnosis. The book is well illustrated and includes an appendix containing 67 case reports and an excellent bibliography (224 entries). This monograph should lessen the difficulty in the clinical diagnosis of these conditions. The author adopts a systematic classification which follows closely those of Cushing and Bailey.

Chapter headings are: (i) Historical; (ii) Classification; (iii) Venous abnormalities; (iv) Arterio-venous angioma; (v) Arterial anomalies; (vi) Syphilitic aneurysm of spinal arteries; (vii) Spontaneous spinal subarachnoid hæmorrhage; (viii) Telangiectases, intramedullary and extradural; (ix) Spontaneous hæmatomyelia; (x) Hæmangioblastomata of the cord; (xi) Extradural hæmangioblastoma; (xii) Lymphangioma; (xiii) The significance of nævi of the skin, lipomata and vertebral anomalies in relation to vascular abnormalities and tumours of the cord.

The work is an important addition to neurological literature.

STRUCTURE AND FUNCTION AS SEEN IN THE FOOT

by F. Wood Jones. London, Baillière, Tindall & Cox, 1944. 329 pages; 150 illustrations. £1 5s. [£1.25]

The author's *Principles of anatomy as seen in the hand* has for some years been considered a classic, to be read by all studying anatomy. The present volume is in some measure complementary to it. After an introductory chapter on the terminology involved, and others dealing with the phylogenetic and ontogenetic history of the foot, the author discusses in detail the fascias, bones, joints, muscles and movements, tendons, and nervous and vascular systems. The book is profusely illustrated with line drawings by the author, and each chapter concludes with a select guide to further reading. It is obvious that great care has been taken in the preparation of this work; it is an important contribution to the literature on the foot and will no doubt find a permanent place in anatomical literature.

MIDWIFERY FOR NURSES

by A. W. Bourne. Third edition. London, J. & A. Churchill, 1944. 296 pages; 111 illustrations. 7s. 6d. [£0.375]

This work, by the Consulting Obstetric Surgeon to *Queen Charlotte's Hospital*, gives a full account of the subject of obstetrics as far as it concerns nurses and midwives. The author points out the necessity for some knowledge of anatomy, physiology and bacteriology by those studying midwifery, and he devotes some space to these subjects. A description of the foetus at various ages is followed by an account of pregnancy—its diagnosis, hygiene and complications. Particular attention is given to the diet during the ante-natal period. The mechanism and management of labour are described in detail and its complications are discussed. The chapter on the management of the puerperium includes a description of some systematic exercises for use during that period. The book, which is adequately illustrated, concludes with instructions regarding the care and feeding of normal infants.

ELEMENTARY HYGIENE FOR NURSES

by H. C. R. Darling. Eighth edition. London, J. & A. Churchill, 1944. 291 pages; 69 illustrations. 6s. [£0.3]

This is written primarily for those nurses studying for examinations or who have been out of touch with a training school for some years; it should also prove a useful text to others interested in hygiene—students, teachers, etc. The book deals principally with the preventive aspect of nursing and is designed to cover the requirements of the final examination of the Australian Trained Nurses' Association.

Chapter headings are: (i) Ventilation, warmth, light, dust, humidity; (ii) Food and milk; (iii) Dietetic treatment of diabetes, epilepsy and obesity; (iv) Water, sanitation of buildings and drainage; (v) Sewage, sanitary inspection of dwellings and temporary hospitals; (vi) Prevention of infectious diseases; (vii) Immunity against infectious disease; (viii) Parasites and insects; (ix) Noxious insects; (x) Personal hygiene; (xi) Health nursing. Some good illustrations are included, and an appendix contains a number of tables and much other useful information.

NURSING IN TIME OF WAR

by P. H. Mitchiner & E. E. P. MacManus. Second edition. London, J. & A. Churchill, 1943. 146 pages; 27 illustrations. 2s. [£0.1]

This booklet, by a Surgeon and a Hospital Matron, and small enough to be carried in the pocket, is designed for nurses, including those who have been called upon to give their services in this field during the war period and who have had no previous practical experience of the subject. Particular attention is paid to the problems incidental to air raid work and first aid posts. Advice is given on the conversion of civilian buildings to casualty hospital use and on the organization of hut or tent hospitals. The remainder of the book is devoted to an account of the treatment of burns, gas casualties, wounds and wound infection, shock, fractures, and the handling of medical casualties during periods of emergency. The technique of intravenous transfusion and infusion is described, and appendices give lists of equipment required at first aid posts and emergency operating theatres. This second edition incorporates much practical experience gained by the writers during the last few years.

GUIDE TO THE JOURNALS

British Heart Journal

6: January 1944

- Adrenal-sympathetic syndrome: chromaffin tissue tumour with paroxysmal hypertension. (R. MacKeith) 1-12
 Reciprocal beating initiated by ventricular premature systoles. (R. Langendorf, L. N. Katz & A. J. Simon) 13-19
 Heart failure in the aged. (T. H. Howell) 20-22
 A case of myxoma of the left auricle. (R. B. Thompson) 23-26
 Circulatory failure due to vitamin B deficiency. (A. Schott) 27-32
 Cardiac output in man by a direct Fick method: effects of posture, venous pressure change, atropine, and adrenaline. (J. McMichael & E. P. Sharpey-Schafer) 33-40
 The heart in myotonia atrophica. (W. Evans) 41-47
 Synchronous heart sound recording by application of a second channel to the Cossor-Robertson cardiograph. (G. D. Dawson & A. M. Jones) 48-52

British Journal of Children's Diseases

41: January-March 1944

- Acute gastro-enteritis in children: a review of 411 cases, 1936-1943, and a plan of investigation and treatment. (W. Gunn) 1-10
 Diphtheria immunization. (H. W. Swann) 10-12

British Journal of Experimental Pathology

25: February 1944

- Distant tumours produced by 2-amino- and 2-acetyl-amino-fluorene. (F. Bielschowsky) 1-4
 The occurrence of A, B and O blood group substances in pseudo-mucinous ovarian cyst fluids. (W. T. J. Morgan & R. van Heyningen) 5-15
 The serum colloidal gold reaction as a liver function test. (N. F. MacLagan) 15-20
 Comparison between the reactions of acute phase serum with pneumococcus C-polysaccharide and with pneumococcus type 27. (G. Löfström) 21-26

British Journal of Ophthalmology

28: April 1944

- Principles of retinoscopy presented on the basis of the theory of projection. (M. Klein) 157-177
 Case of neurofibroma of the choroid. (P. D. Trevor-Roper) 177-180
 Treatment of hypopyon ulcers with albucid and proflavine. (P. D. Trevor-Roper) 181-184
 A case of exudative and haemorrhagic retinitis, with increased intraocular tension, treated by pilocarpine and thyroid. (A. Landau & J. Ruszkowski) 184-187
 A case of primary chancre of the bulbar conjunctiva. (C. D. Shapland) 187-189
 A case of Adie's syndrome. (T. James) 190-193

28: May 1944

- Retinoscopy in astigmatism. (M. Klein) 205-220
 A case of angoid streaks of the retina. (T. H. Butler) 220-224
 An operation for shrunken socket. (J. Kraus) 224-228
 Report on two pairs of brothers showing Marfan's syndrome. (H. J. Stern) 229-232

- Report of a case of a primary carcinoma of the lacrimal sac. (W. L. Roberts & J. R. Wheeler) 233-236
 A case of rupture of a retinal cyst causing retinal detachment. (C. D. Shapland) 236-241
 Congenital paralysis of both external recti treated by transplantation of eye muscles. (J. A. Magnus) 241-245
 Unilateral follicular conjunctivitis due to *Molluscum contagiosum*. (J. A. Magnus) 245-248

British Journal of Radiology

17: April 1944

- The treatment of carcinoma of the lung: Symposium. (J. L. Livingstone, R. C. Brock, F. Roberts, J. L. Dobbie & W. L. Harrett) 101-109
 New light on the origin of craniofacial. (J. B. Hartley & C. W. F. Burnett) 110-114
 Rectangular teloradiation fields. (M. Lederman, J. R. Clarkson & W. V. Mayneord) 115-118
 Post-operative pneumo-peritoneum. (J. E. Bannett) 119-121
 Instantaneous stereography. (G. L. Rogers) 122-125
 The production of isodose curves and the calculation of energy absorption from standard depth dose data. (W. J. Meredith & G. J. Neary) 126-130

17: May 1944

- The indications for and effects of irradiation of the pituitary gland: Symposium. (E. A. Kahn, A. C. Crooke & J. F. Bromley) 131-139
 The value of the opaque enema and its modifications. (N. P. Henderson) 140-149
 A fine control for kilovoltage of a high-tension generator. (F. S. Stewart) 149-150
 Energy absorption. II. Part I—Integral dose when the whole body is irradiated. (W. V. Mayneord & J. R. Clarkson) 151-157
 Four-inch packing nail in the lung. Case followed for thirteen years. (J. Blair-Hartley) 157-159
 A new integrating dosimeter for x-ray therapy. (F. T. Farmer) 160-162

British Journal of Surgery

31: April 1944

- War surgery in Africa. (W. H. Ogilvie) 313-324
 Mobile neurosurgery in warfare: experiences in the Eighth Army's campaign in Cyrenaica, Tripolitania, and Tunisia. (K. Eden) 324-328
 Studies in the pathology of human 'immersion foot'. (W. Blackwood) 329-350
 The problems and principles of the restoration of limb function following injury, as demonstrated by humeral shaft fractures. (F. S. A. Doran) 351-353
 Carcinoma of ampulla of Vater: successful radical resection. (K. Watson) 358-373
 A case of sulphuric acid burns. (G. W. Cashell, H. B. Shay & D. C. Bodenham) 373-377
 Amputations. (G. Perkins) 377-384
 Fat embolism in war surgery. (J. V. Wilson & C. V. Salisbury) 384-397
 The adreno-sympathetic syndrome with transposition of viscera. (L. R. Broster & R. C. McKeith) 393-395
 Sarcoma of the stomach. (A. E. Forrist, K. E. A. Hughes & R. J. C. Campbell) 395-398
 Observations on the regeneration of the semilunar cartilages in man. (J. S. Smillie) 398-401
 Fracture-dislocation of the base of the fifth metacarpal bone. (B. C. Medley) 402-404

British Medical Journal

1 : 8/4/44

- Symptomless incompatible transfusion and resultant changes in iso-agglutinin titre. (R. Drummond) 483-485
Anxiety: alopecia areata: neuro-fibromatosis: auricular fibrillation: description of a patient. (D. Hubble & C. H. Rogerson) 486-488
A milk-borne outbreak of gastro-enteritis due to *Salmonella dublin*. (P. L. Sutherland & F. M. Berger) 488-490
The early treatment of wounds of the chest in the Middle East. (R. B. Scott) 490-492
Visceral leishmaniasis (kala-azar) in an adult contracted in Malta. (F. E. Lipscomb & M. O. J. Gibson) 492-493
Management of a field surgical unit. (J. Howell & B. McN. Truscott) 501-503

1 : 15/4/44

An Investigation of the Therapeutic Properties of Penicillin: a Report to The Medical Research Council

- A review of the work of a penicillin therapeutic research unit. (R. V. Christie & L. P. Garrod) 513-514
Experiences in the systematic administration of penicillin. (H. V. Morgan, R. V. Christie & I. A. Roxburgh) 515-516
Surgery and penicillin in mandibular infection. (R. Mowlem) 517-519
Penicillin in bone infections. (I. M. Robertson) 519-521
The local application of penicillin in soft-tissue lesions. (J. N. Barron & O. T. Mansfield) 521-523
Local treatment of breast abscess with penicillin. (D. B. Fraser) 523-524
Penicillin in treatment of certain diseases of the skin. (I. A. Roxburgh, R. V. Christie & A. C. Roxburgh) 524-528
The laboratory control of penicillin treatment. (L. P. Garrod) 528-530

1 : 22/4/44

- The aetiology of post-arsphenamine jaundice. (J. Beattie & J. Marshall) 547-550
What is psychiatry? (A. Gregg) 550-553
Ocular syndrome in onchocerciasis. (J. G. Scott) 553-554
The nervous complications of infective hepatitis. (F. G. Lescher) 554-556
Surgical problems in forward areas. (G. Blackburn) 556-557

1 : 29/4/44

- War-time incidence and mortality from respiratory tuberculosis. (P. Stocks & E. Lewis-Fanning) 581-583
The relation of dermatology to psychiatry. (F. F. Hellier) 583-585
Sickness records of nurses in a general hospital. (J. Wright) 585-588
Cyclopropane for dental surgery in children. (K. B. Pinson) 588-589
Early secondary repair of complete tears. (P. Malpas) 590

Journal of Hygiene

43 : April 1944

- A statistical examination of the accuracy of vitamin A assays. An analysis of three co-operative experiments designed to ascertain the value of the conversion factor for transforming spectrophotometric values into international units. (J. O. Irwin) 291-314
The sex ratio of pneumonia mortality. (W. J. Martin) 315-327
An atypical *Neisseria* causing meningitis. (J. L. Edwards) 328-329
Studies in immunization by a species antigen. II. The presence of 'species antigen' and of 'opposition factor' in bacteria other than pneumococci. (H. B. Day) 330-336
Revaccination as a measure of immunity to smallpox. (E. S. Horgan & M. A. Haseeb) 337-340
Diphtheria in Glasgow 1934-42. (H. S. Carter) 341-348
A pressure-operated safety circuit for use in high-vacuum serum-drying plants. (F. B. Byrom) 349-351
The use of antiseptic sprays for air sterilization. A summary of a report to the Medical Research Council. (R. J. V. Pulvertaft) 352-356
The epidemiology of Q fever. (E. H. Derrick) 357-361

Journal of Obstetrics and Gynaecology of the British Empire

51 : April 1944

- Some recent studies and investigations in sterility. (A. Sharman) 85-111
The pattern of the contractions of the pregnant uterus under spinal anaesthesia and the attendant changes in the reactivity of the myometrium. (P. Malpas) 112-120
The occurrence and significance of *Clostridium welchii* in the female genital tract. (R. Salm) 121-126
A case of osteomalacia in pregnancy. (H. R. MacLennan) 127-129
Post-clampic kyphosis. (G. Biero) 130-132
The Hogben pregnancy test, with a note on the breeding of *Xenopus* for the test. (F. W. Landgrebe & L. Samson) 133-139
Trichlorethylene and midwifery. (W. Calvert) 140-143
Amyoplasia congenita causing malpresentation of the foetus. (M. I. Ealing) 144-146
Primary melanomasarcoma of the vagina: case report. (Y. M. Bromberg & A. Brzezinski) 147-149
Self-retraction of uterus after Portes operation. (H. Hofmann) 150-151

Journal of Physiology

102 : April 1944

- Anaphylaxis to serum proteins in the guinea-pig. (L. B. Winter) 373-405
A study of dehydration by means of balance experiments. (D. A. K. Black, R. A. McCance & W. F. Young) 406-414
The secretion of urine during dehydration and rehydration. (R. A. McCance, W. F. Young & D. A. K. Black) 415-428
The renal function of newborn infants. (H. Heller) 429-440
The determination of plasma volume by the Evans blue method: the analysis of haemolysed plasma. (C. J. O. R. Morris) 441-445
Changes occurring in plasma and serum on storage and their physiological effects. (H. P. Gilding & M. E. Nutt) 446-470

- Reversibility of carbohydrate and other changes in rats shocked by a clamping technique. (R. E. Haist & J. I. Hamilton) 471-483
Absorption of serum proteins from the intestine of the sensitized guinea-pig. (L. B. Winter) 484-490
The excretion of diiodine by the isolated perfused dog kidney. (A. Hemingway & A. Schweitzer) 491-495

Lancet

1 : 8/4/44

- Toxipathic and trophopathic hepatitis. (H. P. Himsworth & L. E. Glynn) 457-461
Traumatic ischaemia in the forearm and leg. (S. Stanford) 462-463
Diagnosis of adrenal tumours: estimation of 17-ketosteroids in urine. (N. H. Callow & A. C. Crooke) 464-465
Pressure measurement in small anatomical cavities. (D. S. Evans & K. Mendelssohn) 465-466
Bilateral prefrontal leucotomy in Indian patients. (M. V. Govindaswamy & B. N. Balakrishna Rao) 466-468
A case of acute otogenous labyrinthitis and meningitis. (M. Ellis) 468-469
Meningococcal epididymitis. (S. M. Laird) 469-470

1 : 15/4/44

- Posthaemorrhagic fainting: study by cardiac output and forearm flow. (H. Barcroft, O. G. Edholm, J. McMichael & E. P. Sharpey-Schafer) 489-490
Pollomyelitis: studies on the inciting agent and specific serum treatment. (E. C. Rosenow) 491-493
Vitamin K as a prophylactic in 13,000 infants. (J. Lehmann) 493-494
Gingival disease in Gibraltar evacuee children. (J. D. King, A. B. Franchlyn & I. Allen) 495-498
Megalocytic anaemia as a sequel to malaria. (S. F. Seelig & J. R. Hemming) 498-499
Phono-electrocardiography. (G. E. Donovan) 500-501
A case of contracted bladder. (S. I. Levy & J. S. Horn) 501-502
Three and a half years' treatment with sulphapyridine in a case of dermatitis herpetiformis. (B. Barling) 503

1 : 22/4/44

- Analysis of battle casualties admitted to Middle East hospitals. (P. Wiles) 523-525
A base hospital in 1918. (H. J. Nightingale) 525-527
Amblyopia due to a vitamin deficiency. (P. B. Wilkinson & A. King) 528-531
Kala Azar: treated with 4:4' diaminodinitrobenzene. (R. B. U. Somers) 531-533
Malaria as a non-relapsing disease: a review of 1,619 cases in Northern Rhodesia. (L. M. Rodger) 533-534
A nitrous oxide economiser: simple attachment for Boyle's machine. (J. Ives) 534-536
Ulcerative colitis: clinical experiments with pig's intestine. (A. M. Gill) 536-537

1 : 29/4/44

- Forward surgery of abdominal wounds. (W. H. Ogilvie) 555-558
Chronic sinusitis with polypi: A radical external operation. (N. Patterson) 558-560
Chronic sinusitis with polypi: Results of Patterson's operation. (S. W. J. G. Hargrove) 560-562
Regional anaesthesia for surgery of the nose and sinuses. (H. W. L. Dale) 562-563
Treatment of arthritis with acid potassium phosphate. (H. W. Crowe) 563-564
Vaccines and chemotherapy in pneumococcal lobar pneumonia. (A. Dick) 564-565
Nicotinic acid and riboflavin in beef extracts and corned beef. (R. G. Booth & E. C. Barton-Wright) 565-567

Proceedings of the Royal Society, B

132 : March 1944

- Address of the President at the Anniversary Meeting. (H. Dale) 1-27
Croonian Lecture: Nutrition in relation to bone growth and the nervous system. (E. Mellanby) 28-46
A physico-chemical study of some induced changes in the morphology of *Bacterium lactis aerogenes*: A theory of the balance and adaptive variation of certain enzyme processes in bacteria. (C. N. Hinshelwood & R. M. Lodge) 47-67
The pigmentary effector system. X. Relation of colour change to surface absorption of radiation. (L. Hogben & R. L. Kirk) 68-82
Synthetic oestrogenic compounds related to stilbene and diphenylethane. II. (E. C. Dodds, L. Goldberg, E. L. Grünfeld, W. Lawson, C. M. Saffer & R. Robinson) 83-101
The nature of normal trichromatic and dichromatic vision. (F. H. G. Pitt) 101-117

Quarterly Journal of Experimental Physiology

32 : March 1944

- Changes in the circulating blood in man following blood loss or transfusion of concentrated red cells. (M. Dyson, G. Plaut & J. Vaughan) 255-267
Metabolism of liver slices after burning. (E. J. Clark & R. J. Rossiter) 269-277
Carbohydrate metabolism after burning. (E. J. Clark & R. J. Rossiter) 279-300
Subcutaneous temperatures in moderate temperature burns. (K. Mendelssohn & R. J. Rossiter) 301-308
The influence of metabolic stimulants on wound healing: the influence of thyroid and 2-4-dinitrophenol. (T. H. C. Barclay, D. P. Cuthbertson & A. Isaacs) 309-315

Quarterly Journal of Medicine

13 : January 1944

- Myasthenia gravis: a consideration of its causation in a study of fourteen cases. (A. Wilson & H. B. Stonor) 1-18
Serum-iron in health and disease. (J. F. Powell) 19-26
Loss of weight in obese patients on submaintenance diets and the effect of variation in the ratio of carbohydrate to fat in the diet. (A. B. Anderson) 27-36

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HEARING AND SPEECH

SPECIAL CONTRIBUTIONS

DEVELOPMENT OF OTO-LARYNGOLOGY IN BRITAIN	
by Dr. Douglas Guthrie	116
RESEARCH IN OTOLOGY	
by Dr. C. S. Hallpike	119
THE SCOPE OF SPEECH THERAPY	
by Dr. E. J. Boome	121
PIONEERS IN THE TEACHING OF THE DEAF	
by Dr. Douglas Guthrie	122

REVIEW OF SELECTED PAPERS

Nutritional and Endocrine Factors

Influence of Vitamins and Hormones on the Physiology and Pathology of the Ear, Nose and Throat	123
---	-----

Deaf-Mutism

Deafness in Infancy and Early Childhood	124
Deafness in Childhood and Adolescence	124
Discussion on Deaf-Mutism	125

Concussion Deafness

Deafness Resulting from Gunfire and Explosions	126
---	-----

Vestibular Function

Studies in Human Vestibular Function	126
Investigation of Ménière's Disease	127
Treatment of Ménière's Disease	127

Speech and its Defects

Audibility of the Radio Voice	127
Speech Defects	128
Speech Therapy for Certain Vocal Disorders... ..	128

BOOKS, MEMORANDA, REPORTS	129
----------------------------------	-----

GUIDE TO THE JOURNALS	133
------------------------------	-----

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In this number appears the fourth in the series of occasional articles on "The Development of Medical Studies in Britain." The author, Dr. Douglas Guthrie, has achieved a reputation both as a specialist in oto-laryngology and as a medical historian, and therefore has exceptional qualifications for writing on the historical aspect of this special branch of medicine. He has previously contributed an article on "Medicine and Speech" (BMB 96), and in the present number he contributes also a short historical note on the education of the deaf—a subject upon which relatively little has been written.

Dr. C. S. Hallpike is a whole-time member of the scientific staff of the Medical Research Council and Aural Physician to the National Hospital, Queen Square. He has been appointed director of a newly established otological research unit which is to be maintained jointly by the Council and the Hospital. Dr. Hallpike has been a Foulerton Research Fellow of the Royal Society and a Rockefeller Travelling Fellow, and he is the author of a number of papers on the physiology and pathology of the ear.

Dr. E. J. Boome is a Principal Assistant Medical Officer of the London County Council and is in charge of the Council's speech therapy. He is President of the Association of Speech Therapists and a Founder Fellow of the College of Speech Therapists, which has just been formed by the amalgamation of the Association of Speech Therapists and the British Society of Speech Therapists. Dr. Boome is part author of "Nature and Treatment of Stammering," "Relaxation in Everyday Life," "Abnormal Speech" and the remedial chapter in "Spoken English" edited by J. Compton. He has taken a prominent part in drawing attention to the need for the treatment of speech defects and in promoting the organisation and recognition of speech therapy as an auxiliary profession.

SPECIAL CONTRIBUTIONS

372

THE DEVELOPMENT OF MEDICAL STUDIES IN BRITAIN : IV. OTO-LARYNGOLOGY

DOUGLAS GUTHRIE, M.D., F.R.C.S.Ed.

Oto-laryngology comprises not only the diseases of the ear (otology) and of the larynx (laryngology), as the name implies, but also those of the throat or pharynx, of the nose and paranasal sinuses (rhinology) and of the œsophagus, trachea and bronchi (peroral endoscopy). It is open to question whether the present combination will be permanent.

Affections of the ear, nose and throat are mentioned in many of the earliest medical writings, as, for example, those of Hippocrates, Celsus and Galen, but the remedies were then empiric, and it was not until the anatomists of the Renaissance had provided a solid foundation that any real progress was made, the intricacies of aural anatomy having provided a fruitful field for investigation.

The Importance of Anatomy

Vesalius, who revolutionised anatomy by describing what he saw, and not what he expected to see, was succeeded as Professor at Padua by Fallopius whose name, like that of his contemporary Eustachius, became a household word in anatomy. The *Epistola de auditu organo*, 1564, of Eustachius is probably the earliest complete work dealing with the ear. Another early text-book of otology was *De auditu instrumento*, 1573, by Volcher Coiter of Gröningen. This was followed by the work of Mercurialis of Bologna, entitled *De oculorum et aurium affectibus praelectiones*, 1584, and by *De visione, voce et auditu*, 1600, by Fabricius of Acquapendente. Such grouping of otology, first with ophthalmology, then also with laryngology, is a significant forecast of subsequent events.

When the vogue for specialism made its appearance in the nineteenth century, diseases of the ear, nose and throat did not at once become the group as now recognised. The older specialty of ophthalmology enlarged its scope by admitting otology, so that the "eye and ear surgeon" was not uncommon, and there were even stranger combinations. For example, H. Macnaughton Jones (1863) was distinguished in London as a gynaecologist and otologist and J. Kirk Duncanson (1872) of Edinburgh embraced no less than three special branches, when he became known as "the oculo-aural accoucheur."

The Foundations of Oto-Laryngology in the Seventeenth Century

Little advance was made in our knowledge of the ear, nose and throat so long as the old conceptions of anatomy and physiology prevailed. We have noted that the pioneer anatomists broke from the traditions of Galen, which had been followed for a thousand years. The first book dealing with the ear to be printed in English was a translation (1748) of the small work by J. G. Duverney of Paris, originally published in French in 1683.⁸ Duverney corrected an age-long error by proving that the Eustachian tube was not an

avenue of breathing, nor even of hearing, but existed simply as a means of renewing the air within the tympanum. Thomas Willis, Professor of Medicine at Oxford, who made many original observations and wrote the first accurate account of the anatomy of the nervous system, *Cerebri anatome*, in which the "Circle of Willis" is described, also made a contribution to the embryo science of otology by proving that the cochlea was the most essential part of the organ of hearing. His treatise, which appeared in 1683, is quaintly entitled *Two discourses concerning the soul of brutes*³² and, in Chapter 14, "On the sense of hearing," Willis describes the phenomenon of "hearing better in a noise"—the so-called paracusis of Willis. He tells of "a woman who, though she were deaf, yet as long as a drum were beaten within her chamber, she heard every word perfectly; wherefore her husband kept a drummer as his servant that by that means he might converse with his wife." The illustrations for Willis's work were prepared by Sir Christopher Wren, the designer of St. Paul's Cathedral.

About this time, too, another fallacy was exploded by Richard Lower, also of Oxford, who first transfused blood from one animal to another, and first noted the alteration which the blood undergoes during its passage through the lungs. In 1670 Lower showed that nasal mucus was formed within the nose, and was not a product of the brain, as had been imagined during the centuries when "purging the brain" had been a favourite method of treatment.³⁹

Another important step in rhinology was taken in 1707 by William Cowper, who suggested the operation of drainage, by perforation through the socket of a tooth, of the maxillary sinus, or antrum, which cavity had been described by Nathaniel Highmore in 1651.⁵

Progress during the Eighteenth Century

Steady progress continued during the eighteenth century. The invention in 1724 of the Eustachian catheter by Guyot, postmaster at Versailles, directed further interest towards otology.¹² It is significant that two of the major inventions in oto-laryngology, that of the Eustachian catheter by Guyot, and that of the laryngoscope by Garcia, were made, not by medical men, but by a postmaster and by a teacher of singing. Guyot introduced his catheter through the mouth for the purpose of syringing in order to relieve his own deafness, but his discovery attracted little attention at the time. A few years later (1741) a surgeon of the British Army, Archibald Cleland, devised a catheter which he introduced through the nose,³ and Jonathan Wathen, a London surgeon, independently adopted in 1755 a similar method of syringing out the Eustachian tube "when syringing of the outward ear is without any success."³⁰ Apparently the catheter was employed for lavage long before inflation of air was practised.

As for the laryngology of the eighteenth century, it was largely concerned with descriptions of diphtheria, a disease

which was then very prevalent and fatal. A classical *Account of the sore throat* was published in 1748 by John Fothergill, the Quaker physician and philanthropist of London, although it is uncertain whether he referred to diphtheria or to a malignant form of scarlatina.⁹ Another account of the same disease was written in 1757 by John Huxham, who had studied at Leyden under Boerhaave, and who practised in Plymouth.¹⁷ He was the first to note that diphtheria was sometimes followed by paralysis of the palate. A third classic description, clearly referring to diphtheria, under the name of "Croup," was the work of Francis Home in 1765.¹⁵ Home, like Huxham, had studied at Leyden, and he became the first professor of *Materia Medica* in Edinburgh University.

There is no reference to tracheotomy in these accounts of diphtheria. This operation, originally known as bronchotomy, although frequently mentioned in early medical works, was seldom practised.¹⁰ Even after it was popularised in the nineteenth century by Bretonneau and Trousseau, it was regarded as a dangerous procedure. Indeed, Marshall Hall stated in the *Lancet* in 1859 that "we must regard tracheotomy as a heroic remedy, only appropriate to Herculean forms of disease." Nevertheless, tracheotomy was performed in 1730, apparently for diphtheria, by George Martine of St. Andrews in Scotland. His appears to have been the first recorded tracheotomy in Britain, although three years later a London Surgeon, Chovet by name, performed the operation on a criminal about to be hanged, without, however, saving him from death, as had been hoped.

In these early days laryngology was practised by physicians, and otology by surgeons, until each was differentiated in a special branch and eventually reunited as otolaryngology.

Specialism in the Nineteenth Century

The discovery of the function of the Eustachian tube led to various new methods of treatment. Sir Astley Cooper, the greatest surgeon of his day, recommended puncture of the tympanic membrane "in cases of deafness arising from a closed Eustachian tube" (1801) and the procedure was followed for many years. In 1806 there appeared an excellent work on *Anatomy of the human ear, with a treatise of its diseases*, by J. C. Saunders, Demonstrator of Anatomy at St. Thomas's Hospital, and founder of the Moorfields (Royal London Ophthalmic) Hospital.²⁵ The eye and ear were associated as subjects of study in those days, and it was Saunders who first advised paracentesis, or incision of the drumhead, in acute suppuration of the middle ear.

For the most part, however, knowledge of otology remained crude, and diseases of the ear comprised those curable by syringing, and those incurable by any treatment. The opportunity to profit from the precarious state of the embryonic science of otology led to its exploitation by unqualified persons. One of the most notorious was John Harrison Curtis, who had been a dispenser in the Navy, but had not studied medicine. Curtis married a lady of wealth, established himself in a fashionable part of London, and soon acquired a large practice. In 1816 he founded the first hospital in Europe, and indeed in the world, to be devoted to diseases of the ear, an institute which eventually became the *Royal Ear Hospital*. Nevertheless, he was "profoundly ignorant even of the anatomy of the ear" and it was his practice to syringe the ear in almost every case, using an enormous instrument like a garden syringe. His book on *The physiology and diseases of the ear* is of little value save as a historical landmark.⁸

The fully-qualified medical man who first adopted otology as a specialty in London was James Yearsley, who founded the *Metropolitan Ear and Throat Hospital* in 1838, who invented the artificial drumhead, and who drew attention to the close connection between affections of the ear and those of the throat and nose, some years before adenoids were discovered by Meyer of Copenhagen (1868). Another pioneer, Thomas Buchanan of Hull, wrote a volume entitled *Illustrations of acoustic surgery* (1825), emphasising the importance of inspection of the tympanic membrane as a means of diagnosis.² In 1838, an essay on *The structure, economy and diseases of the ear*, containing interesting facts on comparative anatomy and on acoustics, was published by George Pilcher, Surgeon to St. George's Hospital, London.³⁴ At that time it was the custom for certain general surgeons to practise otology in addition to their regular work. Pilcher was one of them, as also was Sir Astley Cooper at an earlier date.

Three Great Pioneers : Toynbee, Hinton and Wilde

The greatest British pioneer otologist was Joseph Toynbee (1815-66), who showed such special aptitude for anatomy that he was able to apply his knowledge in placing otology upon a sound scientific basis. Toynbee was admitted as a Fellow of the *Royal Society* of London at the age of twenty-six, and his name appears in the first list of Fellows of the *Royal College of Surgeons*. Early in his career, as the result of a wordy warfare with Curtis at the Medical Society of London, he vowed that he would "rescue aural surgery from the hands of quacks." Toynbee was a strenuous worker, making over a thousand beautiful dissections of the ear, and thus founding the Toynbee Collection, which was on view at the *Royal College of Surgeons* Museum until destroyed by enemy action in 1941. He built up a large aural practice in Savile Row, London, and he resided at Wimbledon, then a country village. In 1851, he was elected Aural Surgeon and Lecturer at St. Mary's Hospital, the first general hospital to set aside beds for diseases of the ear, and to institute teaching in the subject. Toynbee devoted much of his time to philanthropic work on behalf of the sick poor, his efforts as a social reformer being continued by his son, Arnold Toynbee, in whose memory the first University Settlement, Toynbee Hall, was founded. Joseph Toynbee's book on *Diseases of the ear* (1860) may be regarded as a medical classic.²⁹ The writer sets out to remedy the lack of appreciation of aural pathology and notes, in many cases, the relationship between post-mortem findings and the symptoms present during life. He was the first to describe otosclerosis, recognising "ankylosis of the stapes to the fenestra ovalis" in 160 specimens. Accurate tests of hearing were not in use at that time. Like Astley Cooper, Toynbee punctured the tympanic membrane in selected cases of deafness, but he was able to demonstrate only one example of organic stricture of the Eustachian tube among his specimens. For acute otitis, Toynbee recommended "copious syringing with warm water"; mastoiditis was not treated surgically, and, as might be expected, the mortality was high. It was Toynbee who invented the otoscope or auscultation tube, used as an aid to diagnosis during catheter inflation of the tympanum. As an original thinker, ahead of his time, Toynbee must be regarded as "the father of British otology."^{12, 23} His death at the age of fifty-one was the result of an experiment upon himself, to ascertain the effect of chloroform and prussic acid upon the ear. Thus he was a martyr in the interest of the science he served so well.

Scarcely less worthy was his assistant and successor, James Hinton (1822-75), who is perhaps chiefly remembered as a philosopher, and as the author of *The mystery of pain*, rather than as an otologist. Nevertheless Hinton, who became Aural Surgeon to Guy's Hospital, was no mere satellite of Toynbee. He was probably the first surgeon in Britain (1868) to operate upon a case of mastoiditis, the patient being a man, 58 years of age. Hinton describes the case in his work on *The questions of aural surgery*, 1874.¹⁴ In explaining the somewhat curious title of this work, he stated that he had paid special attention to the unsolved problems of otology. Hinton also improved upon the work of Toynbee in advising early incision of the tympanic membrane in acute otitis media. "This relieves pain, preserves the hearing and diminishes the risk." He further corrected Toynbee in classifying aural polypi, not as growths of the meatus, but of the tympanum. He uttered a warning against unskilful efforts to remove foreign bodies, and he advised careful attention to any ear disease of childhood. His biography, by Ellice Hopkins, gives an intimate and interesting picture of the man and his work.¹⁶ Hinton was succeeded in practice by Sir William Dalby and he in turn by Arthur Cheate, who amplified and catalogued the Toynbee collection.

Contemporary with Toynbee, indeed born in the same year, was Sir William R. Wilde (1815-76) of Dublin, the father of Oscar Wilde, who shares with Toynbee and Hinton the credit of establishing British otology on a sound anatomical and pathological basis. A man of varied interests, he was celebrated as an antiquarian and as a statistician. In early life he settled in Dublin and devoted his first savings to the establishment (1841), in a disused stable, of a dispensary for eye and ear diseases which eventually became St. Mark's Hospital. In this primitive institution he was the first to teach otology in the United Kingdom. Students came to him from all over the world, and particularly from America. Although Wilde also practised ophthalmology,

his chief interest was always otology. His volume on *Aural surgery* (1853) was the fruit of long and patient clinical observation, for Wilde was as essentially a clinician as Toynbee was a scientist, and each gave the other full credit for his work.³¹ The name of Wilde is associated with a snare for the removal of aural polypi, and also with the method of treating mastoiditis by post-aural incision—"Wilde's incision"—an important step towards the modern mastoid operation. The clinical records with which Wilde supports his contentions are models of clear reporting, so that his book may still be read with profit. Interesting details of the life and times of Sir William Wilde may be found in the recent biography entitled *Victorian doctor*.³²

Two subsequent British pioneers of otology, both of them also general surgeons, were Sir Charles Ballance (1856–1936) of London, noted for his work on mastoiditis and on facial paralysis,¹ and Sir William Macewen (1848–1924) of Glasgow, the results of whose operations for otogenic cerebral abscess are still remarkable.²¹

The Evolution and Application of Laryngoscopy

Laryngology did not emerge as a special branch of medicine until the middle of the nineteenth century, when it received a great impetus from the discovery of the laryngoscope in 1854 by Manuel Garcia, a singing master of Paris. Garcia was curious to investigate the action of his own vocal chords, although he had no idea that his invention would become so important in medicine. In his later years he made his home in London, where he died in 1906 at the age of 101.

There had been previous attempts to view the larynx by means of prisms or mirrors, both by British and by Continental observers. In 1829 Babington, of London, demonstrated a "glottiscope" resembling the modern laryngoscopic mirror; in 1837 Liston, the first surgeon to use ether anaesthesia in London, advised the use of a dental mirror to view growths of the larynx; in 1844, Warden, of Edinburgh, suggested the use of prisms to illuminate body cavities; and in the same year Avery, of London, used a throat speculum, in which a mirror was fixed, to secure a view of the larynx.¹⁸

None of those early efforts attracted much attention, and even the method of Garcia, expounded to the *Royal Society* of London, was received with apathy or incredulity; the value of the procedure being first recognised in Vienna.

Laryngology came into being as a branch of general medicine rather than as an off-shoot of surgery. Indeed, the special institution founded in 1863, in Golden Square, London, by Morell Mackenzie, was originally named the "Hospital for Diseases of the Throat and Chest," although the word "Chest" was soon eliminated. "Golden Square," as it was familiarly called, very soon became regarded as the Mecca of laryngology.

Sir Morell Mackenzie (1837–92), who may be regarded as the founder of British laryngology, was born at Leytonstone, Essex, where his father was a medical practitioner. After graduating in London, he studied for over a year in Paris and Vienna, learning the use of the laryngoscope, which had been newly introduced into medicine. Returning to London, he devoted himself to this new branch of medical science, and he soon acquired a large practice and world-wide fame. His essay *On the pathology and treatment of diseases of the larynx* gained for him the Jacksonian Prize of the *Royal College of Surgeons*. A few years later, in 1870, he was able to report the results of his treatment of 100 consecutive cases of growths of the larynx. This alone was evidence of the manual dexterity for which he was famed, a dexterity more remarkable when we remember that cocaine anaesthesia was a later development, and was not then available. Mackenzie wrote treatises on diphtheria (1879), which he proved to be identical with "croup," and on hay-fever (1884), condemning the meddlesome nasal surgery which was then in vogue. In 1887, he founded the *Journal of Laryngology and Otology*, which still flourishes as the sole British journal devoted to the specialty. His greatest work for posterity, however, was his text-book of *Diseases of the throat and nose*, of which the first volume appeared in 1880, the second in 1884. The fruit of long experience and unremitting study, the book remains to this day the basis of all British laryngological literature, and it is still well worth reading.²²

Sir Morell Mackenzie died of tuberculosis at the age of fifty-five, his death having been accelerated by the unfortunate controversy which clouded his later years.¹⁸ Summoned to Berlin in 1887, to attend the Emperor Frederick III, who

suffered from cancer of the larynx, Mackenzie may have erred, as many have done since then, in attaching too much importance to the three negative reports, in this case by Virchow, on the microscopic appearances of tissue removed for examination. At all events, no radical operation was attempted, and the royal patient died a year later. As pointed out by Colledge (1936), in a paper on the subject, the cancerous growth was probably of the rare subglottic variety, a type which had not been differentiated at that day.⁴ The gravity and extent of the lesion was not recognised by any of the medical men in attendance. Mackenzie never denied that the diagnosis might be cancer; he simply gave a verdict of "not proven." Mackenzie faced with dignity the bitter attacks by his German colleagues upon his personal character and his professional skill, although he was doubtless ill-advised in publishing a popular vindication of his conduct in the book entitled *Frederick the Noble* (1888), which greatly accentuated the controversy.²³ Although his name is invariably linked with this case, it must never be forgotten that Morell Mackenzie was the leading pioneer of British laryngology, and that he took a large part in the creation of this branch of medical science.⁷

Another eminent man, who may be claimed as a British laryngologist although he was of German birth, was Sir Felix Semon (1849–1921). Arriving in London in 1878, as a young and unknown foreigner, to study under Sir Morell Mackenzie, he became Mackenzie's assistant and a member of the staff of the Golden Square Hospital. He settled in practice in London and eventually rose to a position of world-wide fame as a laryngologist.²⁴

Perhaps the main reason of Semon's outstanding success, apart from his ability and industry, was his devotion to general medicine while pursuing his work in a newly discovered field. After his appointment as laryngologist to *St. Thomas's Hospital* in 1882, he kept in close touch with the medical wards, a circumstance which led to his important discoveries relating to paralysis of the larynx. He showed that in progressive organic lesions the nerves supplying the abductor muscles of the larynx were effected before those of the adductors, a statement since known as "Semon's law." He also did good service by his study of the early signs of cancer of the larynx, and by disproving the fallacy, then prevalent, that the endo-laryngeal removal of innocent growths of the larynx tended to promote malignancy.²⁵ Semon achieved good results—80% recoveries—in the removal of cancer of the larynx by thyrotomy or laryngo-fissure, an operation which had been regarded as dangerous and uncertain until it was re-introduced and perfected by Sir Henry Butlin (1843–1912), who was not only a general surgeon but also a laryngologist of high repute. The surgeon who first performed the operation of excision of the larynx (laryngectomy) for cancer was Sir Patrick Heron Watson (1832–1907) of Edinburgh.

Semon retired in 1911 at the zenith of his career. He had been the recipient of many well-deserved honours, including that of knighthood in 1897. His memory is perpetuated in the "Semon Lectureship in Oto-Laryngology" of the University of London.

The Twentieth Century and the Future of Oto-Laryngology

Semon was one of the last to practise laryngology as an independent specialty. Early in the present century, it merged with otology to become oto-laryngology. The somewhat clumsy term rhinology was abandoned, by general consent, as diseases of the nose had always been grouped with those of the pharynx and larynx. Naturally, some oto-laryngologists still show a preference for the study of the ear, others for the larynx, but none limit their practice so strictly as did the pioneers. Societies, like journals, have been of great value in the advancement of knowledge. The British Laryngological and Rhinological Association, founded by Morell Mackenzie in 1888, extended its scope to include otology in 1895. The Otological Society of the United Kingdom was founded by Sir William Dalby in 1899, the Laryngological Society of London by Semon in 1893. In 1907, all those Societies became amalgamated in the Sections of Otology and of Laryngology of the *Royal Society of Medicine*, while the Scottish Society of Otology and Laryngology was established to represent the specialty in Scotland and Northern England.

Oto-laryngology was well and strongly represented in Britain during the early years of the present century, and much useful original work was accomplished. Men like Milligan of Manchester, Fraser of Edinburgh, Gray of Glasgow, and Tweedie of Nottingham advanced our knowledge of the ear; Tilley of London, Watson-Williams of Bristol, and Turner of Edinburgh investigated the nasal sinuses; Hill of London, Kelly of Glasgow, and Paterson of Cardiff were masters of œsophagoscopy; while St. Clair Thomson of London wrote the leading text-book of diseases of the nose and throat.¹⁷

On the future of oto-laryngology it would be idle to speculate. Thirty years ago it was virtually a branch of surgery. Its exponents competed with each other in inventing instruments and devising operations. At the present time

the attitude is distinctly more conservative, partly owing to the earlier and more careful treatment of acute infections, especially in children, partly to the introduction of sulphonamides and other drugs. On the other hand, the scope of the work has been extended by the introduction of bronchoscopy and œsophagoscopy and by the elaboration of the tests of audition and of equilibration. Disorders of speech and voice still offer a wide unexplored field, and there are problems of education of the deaf, which can be solved only by an expert otologist. Whether oto-laryngology will retain its present form, or will again divide into various new branches, or even amalgamate with established branches of surgery—neurological, plastic, thoracic and so on—time alone will show. Certain it is that British oto-laryngology will follow the great traditions of the pioneers.

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373

NOTES ON THE PROGRESS AND FUTURE RÔLE OF RESEARCH IN OTOTOLOGY

C. S. HALLPIKE, M.B., M.R.C.P., F.R.C.S.

The relief by surgical measures of suppuration in the middle ear cleft has been for many years a major concern in the work of otologists. This work has been effective and of prime importance; nevertheless, it seems right to point out that the success achieved owes more to the application of general surgical principles than to any advance in fundamental knowledge of the ear. As surgical technique has advanced, there has been a steady decline in the need for its use, and the performance of mastoid operations of all kinds which was common twenty years ago has to-day become a comparative rarity. This development is also largely independent of the growth of specialised otological knowledge, and is attributable to improvement in nutritional standards, chemotherapy and other factors.

That so much of the work of otologists has been accomplished with so little recourse to weapons placed in their hands by otological research helps little to assess the worth of such weapons and implies only that otologists in this particular field of their work have not yet required to advance beyond the stage of general principles. In the next stage of its work otology will need to achieve a higher standard of special knowledge.

The otologist of to-day, and still more of the future, will be called upon less and less to deal by surgery with acute infection of the middle ear cleft and even less with its chronic end-results. Instead, he will need to be increasingly equipped with that special knowledge of aural structure and function which alone can provide a basis for the growth of his understanding of the nature and beginnings of aural, more particularly of labyrinthine, disease.

The further acquisition of such knowledge and its rational application still constitute the formidable agenda of otological research.

Clinical Problems

Ménière's disease, otosclerosis, catarrhal otitis media and inherited deafness are clinical conditions which commonly confront the otologist, and are selected as being serious in their effects, ill understood, and resistant to treatment.

Ménière's disease. Ménière's disease is of particular interest as a subject in which recent developments in pathological anatomy have illustrated the elementary weaknesses of otological research. Until 1938, little was known of the pathological basis of this disorder. Since that date, histological examinations of the labyrinth by Hallpike, Cairns, Rollin and others have clearly established the existence of an obstructive distention of the endolymph system. In this we see that simple observations of structural change of the kind which in 1855 revealed the pathological basis of Addison's disease have only recently been possible in the case of a common disease of the labyrinth.

That otologists should be so far behind in so elementary a field of investigation is due, as we know too well, to the intrinsic difficulties of obtaining the necessary material and of its competent preparation for microscopic examination. These difficulties have not yet been overcome. Far too little material is still examined and not always with the full technical competence which is required.

If we consider now the physiological data which have to serve us in explaining the pathological anatomy of Ménière's

disease, very few are available. Guild's (1927) paper on the circulation of the mammalian endolymph is still a classic, while more recent estimations of osmotic pressure by Aldred, Hallpike & Ledoux (1940) provide a promising indication of the physico-chemical factors which may be involved. Little else is available and neither of these investigations appears to have been confirmed or even repeated. This and much other experimental work on the physiology and pathology of the endolymph are needed, as also a fuller analysis of the clinical features of Ménière's disease.

Otosclerosis. The clinical and histological features of this serious cause of deafness are well known. Its aetiology remains obscure, and a factor in this obscurity is the exceptional difficulty of an experimental approach. Since the work of Wittmaack on the experimental production of otosclerosis in hens, the greatest promise has been provided by Mellanby's * (1938) demonstration of the striking effects upon the bony capsule of the labyrinth in certain laboratory animals of avitaminosis-A. While it is generally recognized that there are many more points of difference than agreement between the bony changes which Mellanby described and those in otosclerosis, it would still seem a possibility that the end of this story has not yet been heard.

The interesting and important work of Holmgren and his English followers on the surgical improvement of hearing in otosclerosis by means of fenestration operations continues to be disappointing, although better results have been claimed by Lempert of New York. It is difficult to avoid the impression that a better understanding of the physiological mechanism which underlies the immediate improvement of hearing would do much to explain and possibly prevent its subsequent regression.

Chronic catarrhal otitis media. The mechanisms which control the output and circulation of the mucus and other fluids of the middle ear constitute an important chapter of ear physiology. Their disturbance under the pathological conditions of catarrhal infection, often in the presence of eustachian insufficiency, underlies and leads to the state which we know as chronic catarrhal otitis media. This condition is common, resistant to treatment, and an important cause of severe deafness, often with involvement of the internal ear. There seems good reason for hope that progress in its understanding and clinical management will in future be furthered by the methods of investigation which have been applied with success, both in this country and America, to the problems of vacuum otitis in Air Force and Naval personnel.

Inherited deafness. It is commonly realized that inherited disease does not of necessity involve a congenital anatomical defect. What is more often inherited is a predisposition to later degeneration of certain tissues or organs. While such degeneration may be inevitable, it is possible also that it may be precipitated by biological factors which may be identifiable and conceivably subject to some kind of control. It is of interest in this connection to note that Grüneberg, Hallpike & Ledoux (1940), in their study of the development of the cochlear changes in a form of inherited deafness found in the shaker mouse, were able to show that no congenital defect of structure occurs here. Instead, a degeneration of a fully formed organ is seen.

Electro-Acoustics and the Otologist

The traditional clinical tests of cochlear function by voice and tuning fork can boast of no great precision. The design of electro-acoustic equipment for the purpose of these tests presents little difficulty from the viewpoint of electro-acoustic technology, and the use of such equipment has long appeared to promise greater accuracy and ease of reproduction of test results.

Gramophone and pure tone audiometers have been well known in Britain for a number of years, without, it must be said, coming into very common use. Here it needs to be emphasized that a major factor in limiting the wider acceptance of audiometers has been the neglect of adequate provision for their calibration. Concerning the functional significance of the tests for which these instruments are used, some discussion still hinges upon the relative value to the clinician of the tests of hearing for speech and pure tones.

At the present stage such discussion would appear to possess little practical significance.

Each variety of test deals with a particular aspect of hearing. Both need to be tested and both tests are probably necessary. The need of the moment is therefore much more that both tests should be brought into common use under conditions which ensure the proper calibration (and its maintenance) of the test equipment.

Concerning the problems which arise in connection with hearing aids, there is an outstanding need that otologists should intervene more generally and much more effectively in assessing the clinical value of these instruments and in the prescription of their use.

In no way can otologists do more to bring this about and so lay a firm foundation for the extension of their knowledge in this difficult field than by taking the lead in the design and standardization of new tests of hearing and test equipment based upon up-to-date electro-acoustic practice, and by ensuring throughout that the fullest provisions are made for dealing with the problems of calibration.

Neurology and the Ear

Defects of cochlear function in neurological disorders occur under conditions which are on the whole limited and well defined. We mention, in particular, tumours of the VIIIth cranial nerve and lesions of the mid-brain. To this extent, therefore, the value of their detection and analysis by otologists is limited. Disturbance of vestibular function, on the other hand, occurs in a much wider range of neurological disorders and often under conditions which leave their pathological basis obscure.

The grosser forms of vestibular dysfunction which result from the involvement of the vestibular centres by disseminated sclerosis and neoplastic disease are of course well known. Some novel aspects of the neurological significance of the vestibular tests have lately been revealed by the work of Angyal & Sherman (1942) on the abnormalities which occur in the vestibular responses of schizophrenics and by the work of Spiegel (1932) and of Fitzgerald & Hallpike (1942) on the cortical localization of vestibular function. The work in question conveys a clear suggestion that the classical tests of vestibular function which have been used by otologists since the time of Bárány may in future find a wider usefulness in elucidating the problems of disease of the central nervous system.

The Medical Research Council and Otological Research

The *Medical Research Council* has interested itself for a number of years in the problems of hearing through its Committee on the Physiology of Hearing. The Committee has sponsored a number of publications which include Reports on *The use of hearing aids* (Ewing, Ewing & Littler, 1936), and on *Hearing and speech in deaf children* (Kerridge, 1937).

The *Council* has recently established three committees to further a wide programme of research into the problems of deafness. One of these committees will deal with the medical and surgical problems of deafness; its Chairman is Professor Henry Cohen of the Faculty of Medicine, Liverpool University, and its Secretary, Mr. T. E. Cawthorne, Aural Surgeon to King's College Hospital and author of a number of papers on the medical and surgical treatment of Ménière's disease.

The second committee has been appointed to consider the problems of design and performance of electro-acoustic equipment used in the investigation and alleviation of deafness. Its Chairman is Dr. W. G. Radley, Director of the Research Station of the General Post Office. The Secretary is Dr. T. S. Littler, Lecturer in Acoustics at Manchester University. Dr. Littler has also worked for a number of years in conjunction with Dr. and Mrs. A. W. G. Ewing of the Department of Education of the Deaf at Manchester University upon the physical characteristics of hearing aids.

Problems connected with the education of the deaf will be dealt with by the third committee, which will sit under the chairmanship of Professor F. C. Bartlett, who occupies the Chair of Experimental Psychology at Cambridge. The Secretary of the committee is Dr. A. W. G. Ewing, Director of the Department of the Education of the Deaf at Manchester University.

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374

THE SCOPE OF SPEECH THERAPY

E. J. BOOME, M.B., M.R.C.P., D.P.H.

Disorders of speech have been known through the ages and have often been a subject of ridicule. Many methods have been tried in the cure of stammering, and most of us are familiar with the story of Demosthenes and the pebble. Moses was a stammerer, and for this reason he refused at first to lead the Jewish revolt against the Egyptians. Once he assumed the leadership, his sense of inadequacy ceased and he lost his fear of speech. This situation would seem to have a parallel in the present-day teachings of the relation between the sense of inferiority and stammering.

It is only lately that the seriousness of the disability involved in defective speech has been recognised by medical and educational authorities. Speech therapy in Britain has undergone many vicissitudes but is now becoming more and more freed from charlatanism and is acknowledged as a profession auxiliary to medicine.

It is difficult to arrive at an accurate estimate of the incidence of speech defects, but it is probable that at least 2% of the school population is affected. In 1943, Dr. J. E. A. Underwood, Chief Medical Officer to the Board of Education, estimated the total number of affected children as 135,000-150,000 in England and Wales and 25,000 in Scotland.

It is therefore clear that defective speech is a problem of some magnitude.

The Conditions in which Speech Therapy can be of Benefit

Speech therapy is, generally speaking, the treatment of defects and disorders of speech. It does not include the education of the deaf and the mentally defective. The defects and disorders of voice, speech and language which fall within the province of the speech therapist may be classified as:

- i. *Stammering* (sometimes called stuttering)
- ii. *Alalia* (not arising from deafness or gross mental deficiency)
- iii. *Dyslalia* (a defect of articulate speech of varying degrees of severity, common in childhood)
- iv. *Aphonia* (a) functional (habitual and hysterical)
(b) organic (e.g. arising from laryngeal disease)
(c) post-operative (e.g. after thyroidectomy, laryngectomy)
- v. *Cleft-palate speech*
- vi. *Defects of nasality* (a) excessive nasality (arising from defective occlusion of the nasopharynx during speech)
(b) Insufficient nasality (arising from nasal obstructions, or their after-effects)
- vii. *Aphasia* (allied with alexia and agraphia)
- viii. *Dysarthria*
- ix. *Abnormalities of voice and speech characteristic of certain diseases of the nervous system.*
- x. *Defects of interpretation of spoken language.*

Methods of Speech Therapy

These may be briefly enumerated:

i. Muscular Relaxation

The patient must learn the difference between normal muscular tension and muscular hypertension. The latter is not only a waste of energy but a definite hindrance to specialised muscular action such as is involved in speech.

It is often necessary for the patient to learn to relax muscle by muscle. It is found to be helpful to achieve this through the medium of muscular movement, i.e. contraction and relaxation of muscle. He should then try to relax the body by conscious thought while in a recumbent position.

ii. Psychological Approach

The personality of the speech therapist is very important. The object of the therapist should be to draw out and develop the latent power of the patient and to inspire him with a desire to reach the goal where his language adequately expresses every thought which he wishes to utter. In fact the speech therapist should be a good missionary.

iii. Re-education of Speech and Voice

This is carried out by specific exercises which are designed to give rhythm, flexibility and co-ordination.

iv. Rehabilitation of the Aphasic

The disorder of speech results from lesions of special speech centres in the cerebral cortex, of association fibres deep to those centres, and also from lesions of the motor cortical centres and paths connecting them with the muscles of articulation.

The treatment given aims at the re-education of the actual speech and rehabilitation of the patient.

Patients reach the speech therapist from other departments of hospitals in which a speech clinic exists, from school medical officers, or from private medical practitioners. Speech therapists work under medical direction and are instructed not to accept patients unless they have been referred for treatment by one of these routes. This provision is necessary in order to avoid overlooking organic disease.

Qualifications as a Speech Therapist

A good general education is essential and candidates are expected to have matriculated or to hold school certificates giving exemption from matriculation. Students are not usually accepted for training under eighteen years of age, though this requirement is not rigidly applied during the war. There is no upper age limit but the training involves close study which might prove difficult to candidates over forty years of age, who may also have difficulty in securing appointments. The speech therapist's work is balanced between that of the teacher and social worker and that of the doctor. A speech therapist is not a specialised teacher.

Courses of training are of two to three years' duration, according to the age and experience of the student. The syllabus includes phonetics, anatomy and physiology, neuropathology, psychology, the theory and practice of speech therapy, and other subjects. Clinical instruction and practice are an integral part of the training. The cost of training is about £50 per annum non-resident. There are five recognised training centres situated in London and Glasgow.

Present Organisation of Speech Therapy in Britain

There are approximately 200 qualified speech therapists in the United Kingdom.

The recognised qualifying body in speech therapy is the *College of Speech Therapists*, 86, Harley Street, London, W. 1 which is an amalgamation of the Association of Speech Therapists and the British Society of Speech Therapists. In 1942, this body was recognised by the Board of Registration

of Medical Auxiliaries, and qualified speech therapists are admitted to the National Register of Medical Auxiliaries.

Of about 315 education authorities in England and Wales, about 100 have appointed speech therapists. In Scotland 6 out of 35 authorities have made such appointments.

In some of the larger towns there are hospital speech clinics where adults as well as children can be treated: those who can afford the fees are treated by speech therapists in private practice. These facilities are, however, by no means adequate to meet the needs of the speech-defective population.

Future Development of Speech Therapy

Speech is so fundamental a function that any disability is one of the greatest obstacles to full intellectual and social

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development. Speech therapy must therefore take its place as a recognised and valuable contribution to social service.

If the needs of the speech-defective population are to be covered, it will be necessary:

(i) to extend present facilities to provide for treatment in all schools;

(ii) to provide for children over school age who, for any reason, have not obtained treatment during their years at school;

(iii) to provide for adults, either in hospitals or in evening institutes similar to those organised by the London County Council.

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PIONEERS IN THE TEACHING OF THE DEAF

DOUGLAS GUTHRIE, M.D., F.R.C.S.Ed.

It is perhaps unfortunate that the term "deafness" is applied to a defect of hearing of any degree, ranging from a slight loss, which scarcely affects the capacity of the individual, to a complete absence of the sense of hearing. Total deafness is relatively rare, only about 10% of all cases, but the degree of hearing which remains in children born deaf is usually insufficient for the perception of speech, and this also applies to children whose hearing has been lost through ear disease at an early age, before speech has been acquired. Such children are dumb, as well as deaf, although their vocal organs are normal, the inability to speak arising solely from the fact that the deaf child does not hear speech, and in consequence cannot acquire the power by the usual process of imitation. He is, in fact, deaf and dumb, although the word deaf-mute is more correct and expressive, implying as it does that the dumbness is the direct result of the deafness. In teutonic languages the word dumb (*Ger. dumm*) originally meant stupid, a sense which it still retains in modern American slang. Thus, it is not surprising that in ancient times the deaf child was regarded as a mental defective, and that no attempt was made to educate him to become a useful citizen, until about the sixteenth century.

We do not know who was the first to suggest or to practise the education of deaf-mutes. Some authorities would accord the priority to St. John of Beverley (A.D. 700), who is mentioned by the Venerable Bede, in his *History of the Church of England*, as having taught a dumb young man to speak, although the account does not state whether the dumb man was also deaf.

At a considerably later date, the problem was discussed by Rudolph Agricola (b. 1442) of Gröningen, Holland, by Jerome Cardan (1501-76) of Milan, and by Salomon Alberti (1540-1600) of Nuremberg, but in each case the method used or advised was to teach the deaf "to hear by reading and to speak by writing." There was no exposition of the manual alphabet, nor of lip-reading.

Probably the first person to instruct the deaf in the use of language was the Spanish Benedictine monk, Pedro Ponce de Leon (1520-84), whose writings have been lost, but whose

work was continued by another monk, Juan Pablo Bonet. Bonet's monograph, entitled *Reduccion de las letras, y arte para enseñar a ablar los mudos*, viz. "The reduction of letters [to their phonetic value], and the art of teaching the deaf to speak," was published at Madrid in 1620. It is mentioned by the versatile Sir Kenelm Digby who, in his *Treatise concerning bodies*, 1644, describes how a Spanish lord, born deaf, was taught to speak by a priest, who wrote a book on the subject. Digby notes further that "he could not govern the pitch of his voice; what he delivered he ended in the same key as he began it," that he attentively studied the face of any one who spoke to him, and that he could interpret nothing in the dark. It is an accurate description of the monotonous speech of the deaf, and of the practice of lip-reading.

The first in Britain to devote his attention to the subject was John Bulwer, "The Chirosotherapist," as he was called. Of his life we know little, but his memory survives in a number of quaint works, now rare, and highly prized by collectors. His *Chirologia, or the naturall language of the hand* (1644), deals with gesture as the natural means of communication in man. Various gestures are illustrated, although there is no attempt to construct a finger alphabet. Four years later, Bulwer published another book, entitled *Philocophus; or the deafe and dumbe man's friend*, showing, it is stated, "that a man born deaf and dumb may be taught to heare the sound of words with his eye, and thence learne to speake with his tongue." The writer is careful to add that the tongue is "not the chiefest cause of speech," the jaws, palate, nose and lips all being essential for correct articulation. In addition to this "Ocular Audition," or, as it is now called, "lip-reading," Bulwer notes that the deaf may appreciate music through the medium of their teeth, by "Dentall Audition." Bulwer also forecast the establishment of a "New Academie" for the education of the deaf, a project which was not realised until a hundred years later.

Contesting the priority with Bulwer, though obviously of later date, we find John Wallis, the professor of mathematics

at Oxford, who had already won a great reputation as an authority on cipher writing. Wallis not only published a treatise on speech, *De loquela*, in 1652, but he also made practical use of his ideas in teaching a deaf man, Daniel Whalley, to speak, and he demonstrated the method to the *Royal Society* and to King Charles II. Daniel Defoe refers to Wallis in his *Life and adventures of Mr. Duncan Campbell, a deaf and dumb gentleman*, which appeared in 1720 and is quite in the tradition of the more famous *Robinson Crusoe*. Campbell, it is alleged, was gifted with second sight, and his services as a fortune teller were widely sought in Edinburgh and, later, in London. Defoe illustrates in his work the finger alphabet which Wallis used in addition to writing and articulation.

Contemporary with Wallis was William Holder, a dignitary of the Church, whose wife was a sister of Sir Christopher Wren, and who wrote an interesting monograph on *Elements of speech*, in 1669. In this work, Holder gives an account of the position and movements of the vocal organs in the production of the various vowels and consonants, a description to which little could be added, even to-day. His method of teaching the deaf consisted in demonstrating the mechanism of articulation, assisted by finger spelling, and he also taught lip-reading. Holder added to his reputation by teaching a deaf-mute, Alexander Popham, who, however, relapsed into silence and was again taught to speak by Wallis, to whose work we have referred. There was some dispute between Holder and Wallis regarding the share of each in this success.

Another contemporary was George Dalgarno, a native of Aberdeen, who spent most of his life as a teacher at Oxford, and who published, in 1680, his *Didascalocophus, or, the deaf and dumb man's tutor*. Dalgarno is said to be the first writer who devised and illustrated a complete system of finger spelling. It was a one-handed finger alphabet. Touching the tips of the thumb and fingers in turn denoted A, E, I, O, and U; touching the first joints, B, C, D, F and G; the second joints H, K, L, M and N; and so on. Dalgarno wisely insisted that the finger alphabet should not be replaced by mere sign language, and he taught the deaf reading and writing rather than speech.

The pioneer who insisted on the importance of a purely oral method of teaching was Jan Coenraad Amman, a Swiss physician who practised in Holland, and who published his book, *Surdus loquens* (The speaking deaf) at Amsterdam in 1692. This work, written in Latin, is the foundation of the method now universally approved and practised. The following century witnessed the researches of two eminent teachers of the deaf, the Abbé de l'Épée in France and Heinicke in Germany. Both deserve to be honoured,

though their methods were at variance. Abbé Charles Michel de l'Épée (1712-89) showed unsparing devotion to the interests of the deaf, although most of his attention was centred in the use of signs, and he compiled, though he did not complete, a dictionary of signs for the use of the deaf. At his own expense, he founded a school for the deaf at Paris in 1765. After his death, the school was continued by his successor, Abbé Sicard, and a few years later it became a national institution. Meanwhile, in Germany, Samuel Heinicke (1729-90), pastor of Nautschütz, was engaged in developing the oral method of teaching the deaf which is now everywhere accepted. He believed that speech should be the sole method of instruction and of expression, and he strongly disapproved of the method employed by the Abbé de l'Épée.

The first school for the deaf in Great Britain, and indeed in the world, was a private establishment founded at Edinburgh in 1760 by Thomas Braidwood. Braidwood was assisted by his brother John, their methods remaining a family secret, though it is known that the tongue of the pupil was guided to various positions of articulation by a little silver rod. When Dr. Samuel Johnson visited the school in 1773, there were twelve pupils, "mostly from England, but several from America." In 1783, the Braidwoods removed to London, establishing, in Old Kent Road, a school which was continued by their nephew, Dr. Joseph Watson. Even in his day, visitors who came to learn the methods were not welcomed, so that Dr. Thomas Gallaudet, who came from America to study, was obliged to proceed to Paris, where he was more cordially received by the Abbé Sicard. Gallaudet, on his return to America, established a school for the deaf at Hartford, Connecticut, in 1816.

Another pioneer was Alexander Graham Bell (1847-1922). His father was a teacher of elocution at Edinburgh who, later, went to America in order to lecture on his system of phonetics and "visible speech." Graham Bell succeeded his father as a teacher of the deaf at Boston. His efforts to transmit speech by electric means, for the benefit of the deaf, led to his invention of the telephone in 1872-76.

Denmark was the first country to introduce the compulsory education of deaf children, in 1817. In Great Britain, this step was not taken until 1893, when education of the deaf-mute child between the ages of seven and sixteen became compulsory. In 1937, the age of entry was lowered to five years, although, in the opinion of most authorities, the training of the deaf child should commence earlier than that of the normal child and, indeed, at the earliest possible age. Vocational training of older children is now undertaken in a number of schools for the deaf, while the opportunities of employment for deaf adults have considerably increased.

REVIEW OF SELECTED PAPERS

Nutritional and Endocrine Factors

376

DISCUSSION ON THE INFLUENCE OF VITAMINS AND HORMONES ON THE PHYSIOLOGY AND PATHOLOGY OF THE EAR, NOSE AND THROAT

by E. Mellanby, R. Greene & R. G. Macbeth, *Proceedings of the Royal Society of Medicine*, 36, 621-626, September 1943

In a discussion before the section of Otolaryngology of the *Royal Society of Medicine*, Sir Edward Mellanby (Secretary of the *Medical Research Council*) said that, although there is at present no well-founded evidence that vitamin deficiency is an important factor in any of the clinical conditions found in otology, it must be expected that future relationships will be determined between nutrition and morbid conditions of the ear, nose and throat.

Mellanby referred in some detail to his work (see Mellanby, 1943) on the remarkable effects of experimental vitamin A deficiency in puppies. The bone hyperplasia, which occurs in from three to five months in puppies on vitamin A-deficient diets, but much later in the adult dog, is due to a derangement of osteoblastic and osteoclastic activity as a result of which bones of abnormal texture and shape are produced.

Thus vitamin A seems to control and co-ordinate the actions of these bone cells, while vitamin D is concerned with the calcification and hardening of osteoid tissue. The effects of irregularity of bone growth in A-deficient puppies are evident throughout the central nervous system but particularly in the auditory apparatus. Overgrowth of bone is regularly found in the internal auditory meatus and severe degeneration in both cochlear and vestibular divisions of the 8th cranial nerve follows as the result of pressure. Overgrowth of periosteal bone in the labyrinthine capsule causes the cochlea to be more deeply placed, so that the auditory nerve is lengthened, compressed, and its course made tortuous. The cochlear division is always the more affected and its fibres degenerate completely; the cells of Scarpa's ganglion and the vestibular fibres are more resistant and the latter degenerate on the peripheral side of the injured point only. Later serous labyrinthitis develops, to be followed by degeneration of the organ of Corti. There is evidence that the former can be cured and the latter prevented by administration of vitamin A at this stage, but the nerve degeneration is irreversible. Mellanby pointed out that this work has not yet been shown to have any direct clinical significance.

Dr. Raymond Greene (physician in the *Emergency Medical Service*) drew attention to the developmental relationships between the pharynx, the auditory apparatus and the pituitary gland, and stressed the fact that probably no system of cells

in the body is entirely exempt from the influences of the endocrine glands. In oto-laryngology this influence is displayed most clearly in effects on bone growth and on the mucous membranes. Thus overactivity of the α -cells of the pituitary (gigantism and acromegaly) is associated with abnormal development of the accessory air sinuses, alterations in the shape of the skull and jaws, and enlargement of the larynx which produces a characteristically deep voice. In hypopituitary states, conversely, underdevelopment of the face and sinuses is often seen and the small larynx and high voice of the eunuch are well known. Cranial dystrophies have been clearly related to the anterior pituitary since Keith's classical work (1911) and more recently cranial dysplasia has been found by Mortimer, Wright & Collip (1937) in over 90 % of cases of atrophic rhinitis, many of which were associated with "constitutional deafness." The relationship between the mucous membrane of the nose and the mechanism of sex is said to have been known to Hippocrates. It is generally held that congestive states of the nasal mucosa in women are related to the increased circulation or output of oestrogenic substances, but there is much less agreement on the efficacy of the treatment of atrophic rhinitis with oestrogens. There is evidence to suggest that this condition may be related to abnormal action on skull growth of the anterior pituitary, the hyperaemia being induced by oestrogen which produces a local increase in the production of acetylcholine. Treatment by direct topical application of prostigmin, though frequently effective, is only palliative and any real success depends on the previous treatment of gross sepsis.

Mr. R. G. Macbeth (*Radcliffe Infirmary*, Oxford) described some observations on the effect of ascorbic acid on the incidence and course of infection in the upper respiratory tract and on the frequency and severity of hæmorrhage following sinus, septal, and tonsillar operations. Patients from the Armed Forces treated in an *Emergency Medical Service* hospital were divided into two groups, one group receiving 1,000 mg. of ascorbic acid on each of 4 successive days immediately before operation. It was concluded "that there was probably a generalised lowering of ascorbic acid in members of the Forces and in civilian workers in the winter and early spring; and that there was a relation between this and upper respiratory infections and a tendency to bleed" after operation.

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¹ [see BMB 97, which includes also a brief review of earlier work by the same author]

Deaf-Mutism

The papers reviewed below were read at a Discussion on Deaf-Mutism at the Section of Otology, Royal Society of Medicine, London, on 5th February, 1943.

The object of the discussion was to state the present position of our knowledge of deaf-mutism and to indicate in what respects the training and management of the deaf child might be improved. The first paper deals with children under three years of age, the second with the older child and the adolescent.

Dr. and Mrs. Ewing are the leading authorities in Britain on the teaching of the deaf. At the University of Manchester they are in charge of the Department of the Education of the Deaf, established in 1934. They have each written many papers on the subject and have collaborated in a well-known and valuable book entitled "The handicap of deafness" (London, 1938).

377

DEAFNESS IN INFANCY AND EARLY CHILDHOOD
 by (Mrs.) I. R. Ewing, *Journal of Laryngology and Otology*, 58, 137-142, April 1943

The paper deals with the records of thirty unselected deaf children. Ten of the children were under the age of 2 and twenty were between the ages of 3 and 4 at the first visit.

Fourteen of the children failed to respond to any form of sound stimulation. The other sixteen possessed at least a small island of hearing. Twenty-eight were born deaf, one became deaf from measles at the age of 1, and one from meningitis at the age of 5 months.

Motor development was not retarded in the children who retained a remnant of hearing; all of them could walk alone by the age of 18 months. The totally deaf children, however, showed much slower motor development. Only two could walk at 18 months. Two of them could not sit up alone before the age of 11 months and two others did not walk alone until the age of 2 years. Five others of the totally deaf group could walk only with difficulty when 3 years old.

Regarding adaptive behaviour, which Gesell defines as "general capacity to exploit environment," for example, reaching for a spoon or building with blocks, this does not appear to be altered in deaf children. Retardation was observed in only two of the thirty children under review.

With reference to language, which includes vocalisation, speech, and auditory comprehension, no child of the group had enough hearing to enable a comparison to be made between deaf and hearing children. Nevertheless a study was made of the deaf child's use of voice and of his methods of making known his wants. Twenty-eight of the thirty children were reported by the parents to use their voices naturally in babyhood; only two were abnormally silent, both totally deaf children. In general there were few variations during the first year and the pitch and loudness of the sounds made by deaf children were the same as those of hearing children. At the age of about 18 months, however, the deaf child loses interest in using his voice and tends to become silent, making a noise only when he is angry or afraid.

The voice of the untrained deaf child of 3 to 5 years of age is ugly and harsh. It is at this time that the deaf child uses his voice less and makes known his wants by pointing, pulling, and gesture. This change from vocal expression to gesture is to be deplored. The vocalisation of the baby who can hear, merges into babbling and then into speech.

Language and its expression in speech are not the fruits of teaching, but they give evidence of learning. In the young deaf child, the first essential is that the use of voice and interest in vocal play should be retained, even though he can hear no sound. He must be constantly encouraged to use his voice so that the kinæsthetic sensations may become fixed in the mind and serve as a basis for speech. The deaf child has an urge to vocal expression which must be strongly encouraged. Gesture does not and cannot serve as an adequate form of stimulation for the mind, although it may serve to satisfy bodily wants.

Deaf children show as much intelligence and desire to imitate as do the children who hear. Such behaviour deceives the onlooker, who forgets that intelligence cannot feed upon itself. The growing mastery over speech is denied to the deaf child. He requires more encouragement on that account. He must be taught to apply language, to articulate and to lip read, and this help can be given only by a teacher specially trained for the task.

378

THE NATURE OF DEAF MUTISM—CHILDHOOD AND ADOLESCENCE

by A. W. G. Ewing, *Journal of Laryngology and Otology*, 58, 143-150, April 1943

In a preceding paper by Mrs. Ewing (1943) it was shown that by the age of 3 years the mental development of the deaf child differs greatly from that of the child who can hear and talk. A knowledge of the young deaf child is of great value when we come to study the needs of the child of school age. In America it has been found that deaf pupils of 12 years were comparable in attainment to normal hearing pupils 4 years younger. The author of the present paper records his observation of 109 children admitted to schools for the deaf: 63 % were born deaf; 37 % had acquired deafness; 15 % retained sufficient hearing to hear loud speech and to justify the use of a hearing aid. When the use of the hearing aid was combined with lip-reading it was much more effective. A deaf child who is a proficient lip reader can follow speech with an accuracy approximating to 40 % of that of the normal listener. The hearing aid must not be regarded as a

substitute for lip-reading. If we imagine ourselves trying to learn a completely unknown language through an imperfect telephone and without any text-book, we may form an idea of the difficulties which confront the deaf child. Furthermore, he has no experience of the understanding of words of any kind, nor of the importance of speech.

The author investigated the motor control of 68 deaf children, employing the tests advised by Oseretski and testing 50 normal children as controls. The "motor index," which ranged from 84 to 104 in normal children, was reduced to 80 in partially deaf children, and 74 in totally deaf children. All motor control was not equally affected. In manual dexterity all the deaf children were approximately normal. It was in the capacity to balance the body that the deaf children were defective, and the disability was in proportion to the degree of deafness. Many deaf children are even above the normal standard in manual dexterity.

Tests of intelligence or practical ability were carried out on 150 children who had been severely or totally deaf since infancy. Among deaf children there is a group who show defective practical ability, but the number is not sufficiently large to justify the establishment of special schools for the mentally-backward deaf.

Apart from this group, deaf children are not lacking in intelligence, a fact already proved by Drever and Collins. As regards mental development, it has been clearly shown by Burt (1937) that an average normal child begins school life with the foundations of his education already well laid and that he learns as much at home as at school. The child rapidly educates himself. Much depends upon his opportunities for mental stimulation. The normal child begins to describe and to interpret at about the age of 4. This ability is retarded in deaf children as has been shown by the writer, who applied the Gesell and Terman-Merrill tests to 72 deaf mutes. There was less retardation in 26 children who had heard speech by the regular use of a hearing aid. Even a small experience of hearing speech is a great incentive to linguistic progress. A few deaf mutes attain high standards of performance. One has taken a science degree at Cambridge, another is a civil engineer, a third is at an agricultural college, while two have attended schools for normal girls with success. In each case lip-reading was facilitated with the use of a hearing aid. Spoken or written expression by the pupils had a prominent place in the training, which must always be "a two-way traffic." The criterion to apply to the education of the deaf is—"To what extent are the children learning to enjoy conversation with normal people out of school as well as in school hours?"

There must be no pause or rest for any worker in this field until wide opportunities, now open only to a few, are made available to all deaf children.

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DISCUSSION ON DEAF MUTISM

by P. Franklin, D. Guthrie, I. R. Ewing & A. W. G. Ewing, *Journal of Laryngology and Otology*, 58, 158-165, April 1943

Mr. Philip Franklin, a London otologist, described the results of his work since 1931 at the Deaf Mutes Speech Clinic for pre-school deaf children.

The specialised speech instruction of deaf children should begin as early as twenty months, although such early training is available only at a few centres, such as that described by Mrs. Ewing. The child with total loss of hearing may be taught to appreciate sound vibrations by the sense of touch. Mr. Franklin used an instrument, the Phonotactor, in which the voice at a microphone constitutes the stimulus, and the child feels it by applying his finger tips to the vibrating magnetic plate. This is simply an adaptation of a method used for centuries consisting in the appreciation of laryngeal vibration by the child who is made to feel the larynx of the teacher.

The majority of congenitally deaf children possess slight hearing, in one or both ears. Total deafness is more frequent in acquired cases, especially when the cause is meningitis. In order to detect slight degrees of hearing, the speaker used the audio-amplifier, by means of which a sound may be gradually increased and the degree of amplification noted at the point where the sound is appreciated. Mr. Franklin advocated the stimulation of hearing by gramophone records of street noises, animal noises, nursery rhymes and the like, and suggested that electrical aids to hearing might be applicable to young children.

Mr. Franklin had found the labyrinth tests of value and stated that a nystagmus response to rotation indicated the presence of hearing however slight. The totally deaf showed no nystagmus reaction and no vertigo after rotation in a chair. Early recognition and early education were of great importance in dealing with deaf children.

The next speaker in the Discussion was Dr. Douglas Guthrie, Consulting Aural Surgeon, Edinburgh Royal Hospital for Sick Children. He proposed to deal with (i) education, (ii) employment, and (iii) sign language, each in its application to deaf-mutism.

i. Many cases of deafness in children were seen first by the otologist, who had to decide whether the child was deaf or mentally deficient. Many cases of deafness were untreated until the child reached school age. It was not realised that the education of a deaf child should be commenced as early as three years of age. Early recognition was of the first importance. Yet many otologists had never visited a school for the deaf and were ignorant of the problems involved.

ii. The medical man ought also to take more interest in the possibilities of employment for the deaf. All deaf persons were employable and at the present time most of them were employed. An employer who had experience of deaf employees was usually willing to employ more, as they proved such efficient workers. The fields of employment open to the deaf were still too few—farm work, boot repairing and tailoring for men, dressmaking and laundry for women. Actually it has been shown that no fewer than 340 different occupations were suitable for the deaf. The medical man should be familiar with the possibilities and should be in a position to advise employers who might make use of deaf workers.

iii. The use of sign language was common among the adult deaf, even those who had been taught to speak in special schools. It appeared that so long as finger spelling was used, no great harm was done. It was the use of conventional signs that kept the deaf from rising into the higher realms of thought and culture. There were some who were of opinion that sign language ought to be taught to all children, deaf or hearing, as a second language besides the mother tongue. This was the view of Sir Richard Paget, who was of opinion that speech was originally mouth gesture. The use of sign language appeared to be the sole means of communication with the outer world in totally deaf persons who had not profited from oral training.

Replying to the Discussion, Mrs. Ewing agreed with Mr. Franklin as to the need for stimulating young deaf children, but she disliked the idea of using heavy vibratory apparatus. Also the mere hearing of sounds was of little value. It was words that were important, appreciated by hearing when possible, and always by lip-reading.

¹ [see BMB 377]

Dr. Ewing also replied, stating that the limits of educational attainment were imposed by lack of opportunity and not by deficiency in natural intelligence. There were three centres for vocational training in Britain, but there was scope for extension. As for sign language, he was glad to note that Dr. Guthrie preferred finger spelling to sign language, but there was a tendency among the adult deaf to shorten the effort and resort to a mere system of signs. The deaf mute who depends on signs is very limited in his world of thought.

The next serious defect in the education of the deaf was the lack of opportunity. It was important to incorporate the deaf as far as possible into the normal life and activities of the community and the otologist could be of great service in the attainment of this ideal.

Concussion Deafness

380

DEAFNESS RESULTING FROM GUNFIRE AND EXPLOSIONS

by S. Suggit, *Journal of Laryngology and Otology*, 58, 313-326, August 1943

The author describes the audiometric findings in 69 ears damaged by gunfire: three varieties of audiometric abnormality are defined, and it is suggested that each variety is correlated with a distinct type of pathological change.

i. *Middle ear damage.* As diagnosed by the otoscopic findings of tympanic hæmorrhage or membrane rupture with a negative Rinne test, this is found to be accompanied by a generalised raising of the threshold throughout the frequency spectrum.

The co-existence of a well marked high-tone loss is considered to indicate additional damage to the cochlea. The middle ear element of this audiometric picture shows restoration to normality with healing of the tympanic lesion. The high-tone loss is likely to persist.

ii. *Gradual high-tone loss.* This is considered to be diagnostic of acoustic trauma by gunfire, usually over a period of years. A localised loss at about 4,000 cycles is thought to be an early stage of this condition. Evidence of tympanic damage is usually absent and the audiometric changes are permanent.

iii. *Abrupt high-tone loss.* A sharp drop in the audiometric curve occurs between 2,000 and 4,000 cycles. In severe cases the frequency at which this drop occurs may be as low as 1,000 cycles. This is identified with the detonation deafness of Jaehne (1911), and the present author gives it the name of concussion deafness. In a few cases it is associated with rupture of the tympanic membrane.

The following analysis is given of the findings in 69 ears:

a. Middle ear deafness	18
b. Gradual high-tone loss	9
c. Abrupt high-tone loss	26
d. Mixed middle ear and gradual high-tone loss	6
e. Mixed middle ear and abrupt high-tone loss	9
f. Mixed gradual and abrupt high-tone loss	1

The author also discusses various points connected with the physiology, pathology and mechanics of injury to the ear from explosion blast, and the possible measures for its prevention.

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Vestibular Function

381

STUDIES IN HUMAN VESTIBULAR FUNCTION

I. *Observations on the Directional Preponderance ("Nystagmusbereitschaft") of Caloric Nystagmus resulting from Cerebral Lesions*

by G. Fitzgerald & C. S. Hallpike, *Brain*, 65, 115-137, 1942

II. *Observations on the Directional Preponderance of Caloric Nystagmus ("Nystagmusbereitschaft") resulting from Unilateral Labyrinthectomy*

by T. E. Cawthorne, G. Fitzgerald & C. S. Hallpike, *Brain*, 65, 138-160, 1942

III. *Observations on the Clinical Features of Ménière's Disease: with Special Reference to the Results of Caloric Tests*

by T. E. Cawthorne, G. Fitzgerald & C. S. Hallpike, *Brain*, 65, 161-180, 1942

I. This study and the two which follow come from the Research Unit of the *National Hospital* for Nervous Diseases, Queen Square, London. In 1923 Dusser de Barenne & de Kleyn investigated experimentally in animals changes in vestibular responses after removing one cerebral hemisphere. For example, if the left hemisphere were removed the left labyrinth became hypersensitive to *hot* caloric stimulation while the right labyrinth became hypersensitive to *cold* caloric stimulation. An application of these results to the diagnosis of cerebral lesions was reported in 1928 by de Kleyn & Versteegh, but these workers gave no information on the nature of the lesions shown by clinical, operative, or *post mortem* findings except in one case.

The present writers have attempted to obtain further evidence of the occurrence in the human subject of directional preponderance of induced labyrinthine nystagmus attributed to cerebral lesions. They devised a uniform method of stimulation, using water at a temperature of 30° C. and 44° C. for cold and hot stimulation respectively (the method is fully described in the original paper). After studying the reactions in the normal and in local disease of the labyrinth they investigated the labyrinthine reactions in 20 cases of disease of one cerebral hemisphere. In 10 of these the disease did not affect the temporal lobe and the reactions were normal. In 10 cases of disease of the temporal lobe, however, the reactions gave a specifically abnormal result with "directional preponderance of caloric nystagmus" to the side of the disease. Thus in all cases of disease of the right temporal lobe the right labyrinth was over-active to heat and the left labyrinth over-active to cold. On the other hand, in all cases of disease of the left temporal lobe the left labyrinth was over-active to heat and the right over-active to cold.

These findings provide an important new method of investigating disease of the brain, but the technique is difficult and requires special study.

II. In this study the special methods described in paper I were applied to 9 cases subjected to an operation to destroy one labyrinth. All were suffering from Ménière's disease. Following operation there was complete deafness of the affected ear with an absence of any response to caloric stimulation. In all cases there was a striking change in the reactions of the intact ear after operation. This consisted of an increase of the hot and a diminution of the cold responses. These caloric tests were repeated at intervals and a considerable degree of restoration towards normal was observed. The central mechanisms responsible for these observations are discussed at length with special reference to the earlier work of Bárány (1906, 1907) and Ewald (1892).

III. In this paper the authors give a detailed clinical study of 50 cases of Ménière's disease. Among the many features analysed, foci of infection in the nose and throat were found to be rare. Some impairment of hearing was present in all 50 cases and was bilateral in 43. The caloric reactions were abnormal in 47 cases, the vestibular functions being tested as described in papers I and II. Abnormalities in the reactions were interpreted as unilateral utricular paresis in 10 cases, unilateral canal paresis in 29 cases, and both these together in 8 cases. This new and delicate method of testing the vestibular reactions has evoked a high proportion of abnormalities (94%) in cases of Ménière's disease. The responses are taken to indicate the presence in this disease of parietic lesions of the utricle and external canal.

[The above summaries are only the barest outline of a comprehensive and detailed investigation which is fully reported in the original papers.]

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382

THE INVESTIGATION OF MÉNIÈRE'S DISEASE

by C. S. Hallpike, *Journal of Laryngology and Otology*, 58, 349-362, September 1943

In this paper the author reviews the details and rationale of certain modifications in the technique of the caloric tests proposed by Fitzgerald & Hallpike (1942). The use of both cold and hot stimulation is essential for the demonstration of directional preponderance, a phenomenon first described (as *Nystagmusbereitschaft*) in 1923 by Dusser de Barenne and de Kleyn in connection with experimental lesions of the cerebral hemispheres in rabbits, and later by Fitzgerald & Hallpike in association with lesions of the human temporal lobe.

Directional preponderance may also occur as the result of a unilateral labyrinthine lesion. This it may do in the natural course of Ménière's disease, as first recognised by Vogel in 1929, or it may result from total destruction of one labyrinth by suppurative or surgical exenteration.

In these circumstances, directional preponderance is revealed by a characteristic alteration in the relationship of the cold and hot caloric responses of the intact ear, the former being inhibited and the latter enhanced. This alteration in the caloric responses of the intact labyrinth was described by Cawthorne, Fitzgerald & Hallpike (1942) in a series of 9 cases in which unilateral labyrinth destruction was performed for intractable Ménière's disease.

The alteration corresponds to, and is accompanied by, an exaggeration of the response to ampullo-petal displacement, by rotation, of the endolymph of the external canal.

This effect of unilateral labyrinth destruction upon the rotational responses has been well known since Bárány and was explained by him upon the basis of Ewald's Law* as being the normal response of the isolated external canal and its associated central connections.

The findings of Cawthorne, Fitzgerald & Hallpike have, however, shown that the characteristic alterations in the caloric responses of the intact canal occur only after destruction of the opposite labyrinth. It is therefore regarded as an instance of directional preponderance, a pathological change in the central responses of the canal due to destruction of the opposite labyrinth. In the light of these findings, the author does not regard Ewald's Law as applicable to the external canal of the intact human subject, and he argues that it is the destruction of the utricle which determines the occurrence of directional preponderance.

The results of the caloric tests are analysed in a series of 100 cases of Ménière's disease and compared with the findings of de Kleyn and Versteegh in a similar series published in 1933.

Three main types of abnormal response were encountered:

- i. *Directional preponderance* (21 %).
- ii. *Canal paresis* (49 %). Here there occurs an equal depression in both cold and hot responses of one external canal.
- iii. *Combinations of i and ii*. Such combinations occur with some frequency (18 %) and are recognisable by a characteristic alteration in the pattern of the caloric response.

In 12 of 100 cases the caloric responses were normal.

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* [see BMB 381]

* [Ewald's Law: Rotational stimulation of the external canal evokes endolymph displacements, which may be away from or towards the cupula. According to Ewald's Law the cupula is more sensitive to the latter.

The experimental work upon which Ewald based this Law was carried out upon pigeons.]

THE TREATMENT OF MÉNIÈRE'S DISEASE

by T. E. Cawthorne, *Journal of Laryngology and Otology*, 58, 363-371, September 1943

The author briefly reviews the medical and surgical measures in vogue for the treatment of Ménière's disease. Phenobarbital or hyoscine are regarded as being the most satisfactory drugs, while good results have been obtained with an anti-retentional régime upon the lines advocated by Furstenberg, Lashmet & Lathrop (1934).

Little evidence is found in support of the view that oronasal sepsis or eustachian obstruction play an important rôle in the aetiology of the disorder. Of operative procedures, favourable results have been obtained in both of two patients subjected to drainage of the saccus endolymphaticus by the method of Portmann (1927).

The author describes in detail his method of opening the external canal with dental drills under a magnification of $\times 10$ with a Leitz dissecting microscope. The membranous canal is exposed and a portion is seized with small forceps and removed. No alcohol is injected. The results obtained with this procedure in 52 cases are analysed. In all a complete loss of cochlear and vestibular function was found.

In 48 cases the vertigo was improved, in 22 it was abolished, and it was unchanged in only 4 cases. Tinnitus was improved in 23 cases and not improved in 25.

The author emphasises that distortion of hearing in the affected ear may be as important a disability as deafness. Its relief by labyrinthotomy may be one of the striking benefits of the operation.

Reference is made at some length to recent work on the rehabilitation of patients subjected to labyrinthotomy. For this purpose systematic exercises have been devised by Dr. Cooksey at Horton Emergency Hospital, and the results appear to have been excellent.

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Speech and its Defects

384

AUDIBILITY OF THE RADIO VOICE [DISCUSSION]

by T. B. Jobson, J. Snagge, V. E. Negus, E. P. Fowler, D. Guthrie & E. D. D. Dickson, *Proceedings of the Royal Society of Medicine*, 37, 263-269, April 1944

Dr. T. B. Jobson: There are two points of view to be considered—that of the broadcaster and that of the audience. A frequent cause of inaudibility is a lack of clear enunciation on the part of the announcer, for which the only cure is a study of elocution. Quite apart from broadcasting or acting, people ought to be taught to speak properly. Elocution should be a standard subject in schools.

With regard to the audience, a fairly high proportion of radio listeners are partially deaf. Such persons find it a strain to listen, and their reaction to sounds becomes delayed. Consequently they miss much of what is said, become strained and fatigued, and ultimately they are tired of listening and abandon it. This is especially true of elderly persons. In senile deafness there is not only a loss of hearing but also a delayed interpretation of what is heard, and this factor cannot be measured by the audiometer.

The B.B.C. announcers have an audience of millions. Some can hear the high tones better, others the low tones. Hearing acuity for the higher tones steadily diminishes with age above the age of 30, and this defect becomes apparent in many persons at 50-60 years of age. The majority of listeners can hear a man's voice more easily than a woman's. Slow deliberate speech, though more audible, is apt to be tedious, but there is an optimum rate which should be adopted in broadcasting.

Mr. John Snagge (British Broadcasting Corporation): Deafness in listeners is only part of the problem which faces the announcer. All the various factors which make for clarity in speech, such as emphasis, pausing, speed, and

intonation, must be considered. Moreover, the speech employed must be a standard English, intelligible to all English-speaking people. The slowest speaker is not always the most audible.

Recently an investigation was made of the speed of speech in a number of persons who broadcast. Figures taken over 3-minute periods showed that the speeds of professional broadcasters were greatest. In three minutes, the most rapid news-reader spoke 528 words, the slowest 488. The Prime Minister averaged 400 words, the Archbishop of Canterbury, 325 words. Public oratory is of necessity slower than broadcasting from a studio. The public speaker can gauge his speed from the effect on the audience. If the broadcaster were to speak as though he were on a platform, listeners would be the first to object. The quality of the voice is often more important than the speed. Some voices are merely disturbing and irritating, so that the listener ceases to listen and then imagines that he cannot hear. The broadcaster, unable to emphasise his words by gesture, depends entirely on his voice. Furthermore, he is obliged to be impersonal in conveying news or information. Not only is correct speech essential; there must also be correct timing of pauses. The pause, not only between sentences, but in mid-sentence, has great effect as a means of emphasis. The success of many broadcasters lies not so much in what they say as in the way they say it, using everyday talk in the language and phraseology of the ordinary man.

Mr. V. E. Negus: The range of hearing is attuned to the range of the human voice. The important range appears to be between 500 and 4000 vibrations. Elimination of high tones renders speech unintelligible, and if a receiving set could be devised which cut out the low tones and amplified the high, it would be very useful to persons suffering from high-tone deafness.

Major E. P. Fowler (U.S. Army): The important range is even smaller than Mr. Negus has stated, probably from 800 to 3000. The consonants, especially s, t, and th, are the letters upon which the intelligibility of speech depends. Radio speakers should be taught to give emphasis to the consonants. Listeners who complain that they cannot hear broadcasts are usually affected by high-tone deafness.

Dr. Douglas Guthrie: Pitch is more important than loudness. If a speaker becomes excited, the pitch of his voice tends to rise. Another factor of great importance is the pause, and it must be remembered that about 30 % of our speech consists of pauses, that is, of silence. The average rate of speech is 160 words per minute. Nevertheless the word is an inconstant unit, of varying length. It would be better to count the number of *phonemes* or speech sounds, each of which lasts $\frac{1}{10}$ to $\frac{1}{15}$ of a second. The scientific study of speech has hardly yet begun, although it offers a wide field for investigation by the cathode-ray oscillograph and by other accurate methods of recording.

Air-Commodore E. D. D. Dickson (R.A.F.): Control officers are now taught the correct method of giving orders by the use of gramophone records of their voices which are played back to them so as to make them aware of their faults.

Mr. John Snagge (in reply): Although, in war time, scientific investigation by cathode ray and other methods has not been possible, it is hoped that this may be undertaken in future. Regarding gramophone records, it is impossible to tell, from listening to these, whether a given speaker will be a success at the microphone. The speech must first be recorded. The problem of studio acoustics has been studied and it has been found that the construction of the room or the lining of the walls has little effect upon reception by the distant listener. Some broadcasters prefer to hear themselves when they speak, others do not.

385

SPEECH DEFECTS

by P. Henderson, *Monthly Bulletin of the Ministry of Health and the Emergency Public Health Laboratory Service*, 3, 66-69, May 1944

This is a short review by a medical officer of the Board of Education. The author criticises the terminology used by some speech therapists and calls for a simplification and standardisation of the nomenclature of speech defects. He

classifies the conditions suitable for speech therapy as follows:

- i. *Stammering*
- ii. *Defects of Articulation*
 - a. *Dyslalia (e.g. lispings)*
 - b. *Rhinolalia*
 - (i) *rhinolalia aperta* (defective nasopharyngeal occlusion)
 - (ii) *rhinolalia clausa* (nasal obstruction)
 - c. *Cluttering* (hurried, jumbled speech)
 - d. *Idioglossia* (articulation grossly defective)
 - e. *Dysarthria*
- iii. *Defects of Voice*
 - a. *Aphonia*
 - b. *Dysphonia*
- iv. *Aphasia*

This may be classified (a) neurologically—as motor (expressive) or sensory (receptive)—or (b) psychologically—as nominal, syntactical or semantic.

The author refers briefly to the methods of treatment employed in different conditions. The work of a speech therapist is best done as a member of a team, and it is important that there should be close co-operation with the school medical officer. In some areas, health visitors report defects of speech in children below school age, and the speech therapist visits the parents and advises them. Whenever possible, a speech therapist should work also at the local hospital. In the author's opinion, a school population of about 10,000 justifies the appointment of a whole-time speech therapist.

386

SPEECH THERAPY FOR CERTAIN VOCAL DISORDERS

by M. Badcock, *Journal of Laryngology and Otology*, 57, 101-112, February 1942

Speech therapy is the treatment of defects and disorders of the voice and speech. Three groups of vocal disorder are considered in this paper by a speech therapist:

- i. *Aphonia and Dysphonia of Organic Post-operative Origin*

In operations on the larynx some part or the whole of the voice-producing mechanism may be removed and an entirely new voice-producing technique must be evolved.

Re-creation of the voice after such an operation as laryngofissure depends upon the formation of a fibrous band which replaces the lost tissues. This band makes contact with the vocal cord of the healthy side.

Method of instruction. The patient closes the hands and presses the backs of the fingers together with the hands horizontally in front of the body, level with the chest and a little distance away from it. The therapist tries to draw the hands apart and the patient must resist. This creates the requisite amount of tension to cause the true vocal cords to work. If the pressure and the tension are too great the false cords will be used instead. The therapist must use just enough force to let the patient feel a little resistance.

When complete laryngectomy has been performed the therapist can adopt either of the following courses:

- (a) to teach the patient to use a laryngectomy reed, or
- (b) to teach him œsophageal speech.

(a) *Use of the laryngectomy reed.* The laryngectomy reed is an artificial larynx, consisting of a small metal cylinder which contains a reed. A tube leads from the tracheotomy cannula to the cylinder. Another tube leads from the cylinder to the mouth and is held just inside the lips. Sound from the vibrating reed is converted into speech by the action of the tongue, teeth and lips.

In using the reed, difficulty is often experienced in regulating the breathing during speech, and patients find that the flexible rubber tube in the mouth interferes with articulation.

The patient is told to breathe easily and exhale as slowly and steadily as possible. The reed is then used and he repeats the exercise, feeling the vibrations of the reed in his mouth and regulating his breathing till a satisfactory volume of tone is obtained.

Exercises for mobility and control of the tongue and lips are followed by practice of vowels and consonants. These are studied in a mirror, first while holding in the mouth a piece of rubber tubing exactly corresponding to the mouth-piece of the reed, then while using the reed itself. Easy single-syllable words are followed by short phrases which must be spoken smoothly.

(b) *Œsophageal speech.* This method involves the substitution of controlled eructation for laryngeal speech. The patient is told to close the mouth and to contract the supra- and infra-thyroid muscles, thereby fixing, drawing forward and opening the upper sphincter of the œsophagus, to which the muscles have become attached. Air passes into the upper part of the œsophagus, is retained for a short time and expelled at will with the mouth slightly open. Sound is produced by varying the tension of the sphincter and is modified into speech by the accessory organs of articulation. When the patient can produce sound in this way he modifies it into vowels, combines vowels and consonants and uses single-syllable words and short phrases.

With practice, speech becomes fluent and the voice, though low-pitched and rough, is not repulsive.

ii. *Aphonia and Dysphonia of Functional Origin*

Case histories of these disorders frequently show that there has been some local organic trouble at the time of, or previous to, the onset of the voice defect. The functional aspect of the condition is shown by the possibility of producing a noisy cough. The onset usually follows some shock or severe emotional disturbance.

Complete *aphonia* is characterised by complete abduction of the cords during attempted phonation. In *dysphonia*, normal voice may come intermittently with periods of complete aphonia, or an incomplete degree of adduction is achieved, where tension of the cords is poor, where spasmodic closure of the glottis occurs, or where the ventricular bands are brought into contact as well as, or perhaps instead of, the vocal cords.

The underlying psychological cause of the disorder is always subconscious and unless treated there will be a tendency to relapse.

Method of treatment. (a) It is important to convince the patient that the symptoms are not of organic origin, and to draw attention away from the throat. (b) Correct voice production should be described and induced in the patient by suggestion and persuasion. The hand-pressure method already described is useful in these cases. (c) The psychological aspect of the condition must be investigated, and the patient should be referred to a psychotherapist if necessary.

iii. *Voice Defects Resulting from Severe Deafness*

The object of treatment is to prevent deterioration of the voice.

Method of instruction. By placing the finger-tips lightly on the throat in the region of the larynx during phonation the patient can distinguish variation of pitch and volume. Inflection as well as pitch and volume must eventually be controlled without using the fingers by the patient's memory of voice and by sensations experienced in the larynx and resonance cavities during phonation.

387

BOOKS, MEMORANDA, REPORTS

[The prices quoted are those which obtain within the United Kingdom. Editors of medical journals who wish to review publications of which notices appear below are invited to apply to the Editor for review copies, of which a few are sometimes available. Orders for any of the publications mentioned below may be sent to BES Ltd., 6 Hanover Street, London, W. 1, England, if there are difficulties in obtaining them locally. Publications may be referred to by the numbers used below, preceded by the letters BMB, e.g. BMB 290/5. It should be noted that supplies of all publications are limited and there can be no certainty that publications ordered or requested for review will be available.]

387/33

DISEASES OF THE NOSE, THROAT AND EAR

by I. S. Hall. Third edition. Edinburgh, E. & S. Livingstone, 1944. 459 pages; 90 illustrations. 15s. [£0.75]

A concise account of the subject, written primarily for the senior student and the general practitioner, and providing sufficient information for their ordinary needs. It is divided into six main sections, which deal with the nose, nasal accessory sinuses, pharynx, larynx, endoscopy, and the ear respectively. The more common affections of these organs are discussed in detail and the simple operative procedures are described. The book is well arranged and production is of a high standard; the illustrations, some of which are in colour, are excellent. In this new edition of the book the subject matter has been revised, and a rearrangement of the text has been carried out to facilitate reference. Several additional diagrams and plates have been added. This is an excellent survey of the subject.

387/34

TEXTBOOK OF MEDICAL TREATMENT

by various writers. Edited by D. M. Dunlop, L. S. P. Davidson & J. W. McNee. Third edition. Edinburgh, E. & S. Livingstone, 1944. 1218 pages. £1 10s. [£1.5]

The whole field of medical treatment is covered by this book, which is a collective work, written by a number of authorities, under the editorship of three professors of medicine in Scotland. The contents are arranged under the following main headings: (i) infectious diseases; (ii) clinical use of the sulphonamide drugs; (iii) tuberculosis; (iv) common diseases of the skin; (v) venereal diseases; (vi) common tropical diseases and helminthic infections; (vii) some common disorders in infancy and early childhood; (viii) industrial diseases; (ix) metabolic diseases; (x) diseases of the ductless glands; (xi) diseases of the blood, spleen and lymphatic glands; (xii) diseases of the alimentary canal; (xiii) diseases of the liver, gall-bladder and biliary tract, pancreas and peritoneum; (xiv) diseases of the heart and circulation; (xv) diseases of the blood vessels of the limbs and the effects of cold; (xvi) diseases of the nose, throat and ear; (xvii) diseases of the respiratory system; (xviii) renal diseases; (xix) chronic rheumatic diseases and diseases of bone; (xx) diseases of the nervous system; (xxi) psychotherapy in general practice; (xxii) technical procedures and oxygen therapy.

This new edition has been extensively amended to include the most recent advances in medical therapeutics, especially those in the field of chemotherapy. The sections dealing with cerebrospinal fever, sprue, the hæmorrhagic and hæmolytic diseases of the newborn and of adults, compressed air illness, diabetes of pregnancy, myxœdema, the x-ray treatment of thyrotoxicosis, parathyroid tetany, diabetes insipidus, dyspepsia and the treatment of peptic ulcer, essential hypertension, head injuries, blood transfusion and oxygen therapy have been completely or partly re-written, and new matter has been added on meningococcal septicæmia, spontaneous hypoglycæmia, male hormone therapy, deep x-ray treatment of certain blood diseases, patent ductus arteriosus, the effects of cold, the rhesus factor. Some of the directions for dietetic treatment are impracticable in war-time, and wherever possible the writers have suggested alternative items of food. The book has been written for students and practitioners, in an endeavour to fill the therapeutic gap left by most textbooks on general medicine.

387/35

TEXTBOOK OF HISTOLOGY FOR MEDICAL STUDENTS

by E. E. Hewer. Third edition. London, W. Heinemann (Medical Books), 1944. 364 pages; 344 illustrations. 17s. 6d. [£0.875]

This textbook is written primarily for medical students by one who has had 30 years' experience in teaching them. In its 37 chapters are described and depicted the minute structures of the human body; emphasis is laid on the physiological appearances and their relation to function, rather than on the so-called "normal state." The illustrations, which reach a very high standard, consist of low-power photomicrographs and diagrammatic line drawings. In this new edition some minor revisions bring the text up to date, while a number of new photomicrographs have been added. There is a useful appendix describing the more important histological methods. This is in every respect a well-produced volume and a valuable guide to the study of histology.

387/36

HANDBOOK OF DIAGNOSIS AND TREATMENT OF VENEREAL DISEASES

by A. E. W. McLachlan. Edinburgh, E. & S. Livingstone, 1944. 354 pages; 159 illustrations. 15s. [£0.75]

The author, who is in charge of the Venereal Diseases Department at Newcastle General Hospital, has had much experience in

the instruction of undergraduate and postgraduate students in the subject and is well qualified to write this concise introduction to the principles of diagnosis and treatment of diseases of venereal origin. He points out that in no other department of medicine is there a greater responsibility on the part of the practitioner to maintain a constantly high index of suspicion as to the possible occurrence of a venereal disease, to detect or exclude infection at the earliest possible moment by the routine application of the appropriate laboratory tests, to impress upon the patient the dangers of neglect of treatment, and to carry out adequate treatment and tests of cure in cases of established disease. The book is divided into the following chapters: (i) the course of acquired syphilis; (ii) the diagnosis of primary syphilis; (iii) the diagnosis of early generalised (secondary) syphilis; (iv) the treatment of early syphilis; (v) late generalised syphilis (tertiary syphilis); (vi) syphilis of bones, joints, muscles, tendons and bursae; (vii) cardio-vascular syphilis; (viii) manifestations of syphilis in other viscera, organs, and glands; (ix) neuro-syphilis; (x) the diagnosis and treatment of congenital syphilis; (xi) chancroid; (xii) gonorrhoea in the male (anatomy of male genito-urinary tract); (xiii) diagnosis and treatment of gonorrhoea in the male; (xiv) complications of urethritis in male lower genito-urinary tract; (xv) gonorrhoea in the female (anatomy of the female genito-urinary tract); (xvi) diagnosis and treatment of gonorrhoea in the female; (xvii) gonococcal proctitis; metastatic complications of gonorrhoea; muco-cutaneous manifestations of gonorrhoea; (xviii) vulvovaginitis; (xix) gonococcal infections of the eye; (xx) urethroscopy; (xxi) other conditions commonly referred to venereal diseases departments. Nineteen of the illustrations are in colour.

387/37

MANUAL OF PSYCHOLOGICAL MEDICINE

For Practitioners and Students

by A. F. Tredgold. London, Baillière, Tindall & Cox, 1943. 298 pages. 18s. [£0.9]

The author of this manual is Consulting Physician to *University College Hospital*, London. The book gives a reasonably full account of the many forms of mental abnormality met with in medical practice. After describing the various manifestations of mind, the author discusses the causation and symptomatology of mental disease. Chapters are devoted to the description and treatment of mental instability, anxiety states, hysteria, neuroses and psychoses, neurasthenia. The writer makes a distinction between schizophrenia and dementia præcox, outlines the history of the doctrines regarding them, and briefly refers to their treatment. Further chapters fully describe mental disorders of toxic, febrile, syphilitic and traumatic origin respectively. Other forms of organic disease give rise to mental disorder; a description of these is followed by an account of mental disease associated with ill-bearing. The book concludes with chapters on mental decay and mental and moral defect, an account of psychotherapy, occupational therapy, shock therapy, narcotherapy, and a consideration of the legal and sociological aspects of psychological medicine. The writer obviously has a considerable acquaintance with the history and literature of this very complicated branch of medicine; great care has been taken to present the subject in a clear and readable form. A carefully prepared index is included.

387/38

THE SYMPTOMATIC DIAGNOSIS AND TREATMENT OF GYNÆCOLOGICAL DISORDERS

by M. Moore White. London, H. K. Lewis & Co., 1944. 229 pages; 107 illustrations. 16s. [£0.8]

A large proportion of the gynæcological complaints encountered by the general practitioner comprise minor ones such as pain, backache, leucorrhœa, and disturbances of menstruation. This book is written with the aim of helping the general practitioner in treating women suffering from such ailments and also to enable him correctly to diagnose conditions which might benefit from treatment not usually within his capacity. It is not an exhaustive textbook of gynæcology, although it embodies much useful information and is obviously the work of a writer of large and varied clinical experience. The book is divided into the following chapters: (i) vulval and vaginal disorders; (ii) pruritus vulvæ; (iii) amenorrhœa; (iv) dysmenorrhœa; (v) menorrhagia; (vi) irregular vaginal hæmorrhages; (vii) vaginal discharge; (viii) vaginal and uterine prolapse; (ix) dyspareunia; (x) urinary frequency, incontinence, and retention; (xi) pelvic pain; (xii) backache; (xiii) sterility; (xiv) the menopause; (xv) gynæcological causes of abdominal pain and enlargement; (xvi) distressing antenatal symptoms; (xvii) pre- and post-operative treatment and complications; (xviii) contraception; (xix) radiation therapy in gynæcology. An appendix gives information on the different hormone preparations now available. The author includes some good illustrations.

387/39

THE CONTROL OF CROSS INFECTION IN HOSPITALS

Medical Research Council War Memorandum No. 11. London, H.M. Stationery Office, 1944. 34 pages. 6d. [£0.025]

About a century ago, hospitals were being closed—and in some cases demolished—because of the prevalence of "hospitalism," as wound infection was then described. The improvement re-

sulting from the work of Lister and his successors was so great that attention was distracted from the importance of infections acquired in hospital from other patients, from the medical and nursing staff, or from visitors. Recent work has shown that hospital infection is still a problem of considerable gravity, which affects particularly hospitals for infectious diseases, hospitalised infants, and surgical wards. Transmission of infection may be by persons (immediate and mediate), by droplets, or by ward dust (which may contain virulent organisms).

In 1939, the Preventive Medicine Committee of the *Medical Research Council*, recognising the importance of the problem, appointed a Sub-Committee on Cross Infection in Hospital Wards, which is responsible for the present memorandum. Sir W. Wilson Jameson, Chief Medical Officer of the Ministry of Health, writes an introduction, in which he emphasises the practical importance of the subject. Chapter headings are: (i) prevalence and consequences of cross infection; (ii) sources and modes of infection; (iii) the prevention and control of cross infection, and (iv) procedure following the occurrence of infection in a ward. There are appendices on (a) disinfection and sterilisation, (b) rules for isolation nursing in cell or open ward, (c) special precautions for maternity units, (d) rules for a ward dressing team, (e) application of crude paraffin oil to floors, and (f) course of practical bacteriology for nurses. Finally there is a bibliography containing 7 general and 57 special entries.

This is an exceptionally useful publication.

387/40

DISEASES OF THE CHEST

by R. Coope. Edinburgh, E. & S. Livingstone, 1944. 524 pages; 160 illustrations. £1 5s. [£1.25]

This book has been designed to give the student an introduction to diseases of the chest, and it should not be considered as a manual of reference. It stresses the fundamental principles, in order to give the learner a good basis upon which to build his knowledge, and this means the sacrifice of a great many details which are usually found in more orthodox textbooks. There is a particularly good account of the clinical examination of the patient and of physical signs; those signs which are of real practical importance have been carefully selected for description. The author pays special attention to the principles of treatment and shows a very human insight into the patient's point of view. Altogether this is an excellent book for the student and young practitioner and, although it may appear long, it is very easy to read. Chapter headings are: (i) physiological and anatomical considerations; (ii) symptoms; (iii-v) physical signs—inspection, palpation, percussion, auscultation; (vi) radiology; (vii) collapse of the lung; (viii) foreign bodies in the air passages; (ix) bronchiectasis; (x) bronchial carcinoma and other intrathoracic tumours; (xi) upper respiratory infection—the common cold; (xii) influenza; (xiii) oxygen therapy; (xiv) acute bronchitis; (xv-xvi) chronic bronchitis and emphysema; (xvii-xviii) the pneumonias; (xix) abscess of the lung; (xx) pulmonary tuberculosis; (xxi) uncommon pulmonary infections and other lesions; (xxii) diseases due to the inhalation of dusts, fumes and gases; (xxiii) pulmonary fibrosis; (xxiv) pleuritis; (xxv) empyema; (xxvi) thoracic complications of sub-diaphragmatic infection; (xxvii) pneumothorax; (xxviii) spontaneous hæmothorax, hydrothorax, chylothorax; (xxix) developmental pulmonary cysts; (xxx) asthma; (xxxi) circulatory disturbances of the lungs; (xxxii) chest injuries; (xxxiii) mediastinal lesions; (xxxiv) diaphragmatic lesions. The appendix consists of 32 x-ray plates.

387/41

THEORY OF OCCUPATIONAL THERAPY

by N. A. Haworth & E. M. Macdonald. Second edition. London, Baillière, Tindall & Cox, 1944. 148 pages; 68 illustrations. 7s. 6d. [£0.375]

The term "occupational therapy" came into use during the last war to describe the "work cure," then used principally in mental hospitals. More recently attention has also been focused on the value of active exercise in physical ailments, and occupational therapy is establishing its place in the rehabilitation schemes of both general and special hospitals. The book now reviewed is written primarily for students training as occupational therapists and for nurses who will have the supervision of patients receiving this form of treatment. It gives in detail the application of various crafts to individual illnesses. The occupational therapist should not only have a practical knowledge of occupations suitable for various conditions, but should also understand how to apply these crafts therapeutically and to meet the needs of each individual patient; the information contained in this book adequately covers this requirement and should prove useful to all others, doctors and medical auxiliaries, interested in the subject. The first edition, which appeared in 1940, was the first textbook on occupational therapy to be published in Britain. Its authors have had extensive experience of their subject, particularly with mental cases and in the training of occupational therapists. In the new edition the text has been revised and there is new matter on occupational therapy in a general hospital, the treatment of cardiac cases, head injuries, and arthritis. The book is arranged in the following chapters: (i) introductory; (ii) occupational therapy in the treatment of mental disorders and in mental nursing; (iii) occupational therapy in a general hospital and in orthopaedic, surgical and cardiac cases; (iv) occupational therapy in the treatment of tuberculosis; (v) equipment, apparatus, materials, etc.;

(vi) records, prescriptions, etc.; (vii) finance; (viii) training. In addition, an extensive bibliography covers every aspect of the subject, from anatomy and physiology to manuals on the various crafts described, and a list of suppliers of materials and apparatus is given in an appendix. The book is adequately illustrated.

387/42

MEDICAL PHOTOGRAPHY Radiographic and Clinical

by T. A. Longmore. London, Focal Press, 1944. 425 pages; 160 illustrations. £1 5s. [£1.25]

Information sufficient for an adequate technical knowledge of medical photography, both radiographic and clinical, has until now been scattered among a vast literature on radiology and photography. The author of the above work, who is Instructor at the Army X-Ray School, has brought together for the first time in one volume all the information necessary to provide an adequate working knowledge of this subject. Assuming no previous acquaintance with the subject on the part of the reader, he commences with a description of the photographic process, and arranges the rest of the book in three parts. The first, devoted to radiography, is divided into the following sections: (i) x-ray materials; (ii) x-ray apparatus; (iii) screens and cassettes; (iv) cones and diaphragms; (v) radiographic exposure factors; (vi) the radiographic image; (vii) chemistry of development; (viii) fixing; (ix) methods of processing; (x) rinsing, washing and drying; (xi) tropical processing of x-ray films; (xii) photographic solutions; (xiii) reduction and intensification; (xiv) the x-ray dark-room; (xv) faults in radiographs. Part II deals with clinical photography; in it the principles of the camera are described in detail, followed by sections on (i) negative materials; (ii) light filters; (iii) clinical phototechnique; (iv) reproduction of tone; (v) printing; (vi) processing clinical materials; (vii) after-treatment and finishing. Part III considers the special techniques employed in mass miniature radiography, cineradiography, tomography, x-ray stereoscopy, colour reproduction, stereoscopic photography, simple photomicrography, electrocardiography, and the 16 mm. motion picture camera. The Appendix includes a formulary, tables of weights and measures, details of photographic chemicals and some substitutes for them, and a glossary of terms. The book is profusely illustrated with diagrams, line drawings and half-tones, and is obviously the work of a writer with considerable experience of his subject. Although addressed primarily to radiographers and other medical auxiliaries, it will also be of value to the radiologist and the physician interested in clinical photography.

387/43

REPORT ON A NATIONAL MATERNITY SERVICE

published by the Royal College of Obstetricians and Gynaecologists, 58 Queen Anne Street, London, W.1, 1944. 43 pages. 1s. 6d. [£0.075]

This Report was prepared by the Maternity and Infant Health Services Committee of the Royal College of Obstetricians and Gynaecologists, under the chairmanship of Dr. Eardley Holland. After discussing the present maternity service and its defects it recommends the formation of a national maternity service, embracing all existing services and controlled by a single administrative authority. This integration is considered essential for efficiency.

A maternity service should have three principal aims: (i) to bring the mother safely through pregnancy, labour and puerperium; (ii) to secure the birth of a healthy infant; (iii) to leave the mother as well at the end of the puerperium as she was when she became pregnant. By making better use of present resources, maternal mortality could be considerably lowered.

For the purposes of a national service it is suggested that Britain be divided into areas having populations of about 1,000,000 and yielding about 15,000 births a year. It is also suggested that the country be divided into large health regions in which the service would be based on key or primary centres consisting of not more than 100 maternity beds (with at least one-third of them antenatal beds), antenatal and other clinics, a department for infants under a paediatrician, laboratories, and teaching and research facilities. These key centres would, where possible, be a part of a university or medical school.

In the areas the service would be based on divisional maternity centres closely associated with the key centres, and at the periphery there would be small local centres. The university centres would be the undergraduate schools, and some of the divisional centres would be the postgraduate schools and schools for midwives.

Suggestions are made for the close association of general practitioners with the service through local centres. Qualifications for such work should be special and approved postgraduate experience.

On the social and economic aspects of the problem, the necessity for adequate nutrition during pregnancy and for a high standard of family life is stressed. The problems of the mother in industry are discussed, and the importance of home helps and nurseries is recognised. Importance is also attached to the general health education of children, which should include instruction in sex and parenthood.

387/44

CLINICAL PRACTICE IN INFECTIOUS DISEASES for Students, Practitioners and Medical Officers

by E. H. R. Harries & M. Mitman. Second edition. Edinburgh, E. & S. Livingstone, 1944. 570 pages; 52 illustrations. £1 2s. 6d. [£1.125]

The practical experience of the authors, both medical superintendents of *London County Council* fever hospitals, is combined in this work with an exposition of modern fever practice as reflected in other writings. The preliminary chapters deal with general topics such as the sources and modes of infection, resistance, allergy, diagnosis, laboratory aids and clinical tests. The chapters on individual diseases, twenty-five in number, are grouped primarily into inhalation and ingestion diseases. Haemolytic streptococcal fevers and epidemic diseases of the nervous system form separate sub-groups, each preceded by a description of the features common to the group; the ingestion diseases are similarly introduced. Certain diseases likely to assume increased importance under war conditions (e.g. Weil's disease, the louse-borne infections) are included. Prophylaxis is emphasised throughout; ample attention is given to the management of infectious diseases, and a final chapter deals with their control in hospitals. Chapters on Isolation and Chemotherapy appear for the first time in the new edition, which shows other signs of considerable enlargement and careful revision, including, at the end of each chapter, references for further reading. The authors consider that half-tone or colour plate illustrations of the exanthemata are rarely of any value to the student; illustrations in this book therefore consist of line and colour diagrams.

387/45

COMBINED TEXTBOOK OF OBSTETRICS AND GYNAECOLOGY for Students and Medical Practitioners

revised by J. M. Munro Kerr, R. W. Johnstone, J. Young, J. Hendry, D. McIntyre, D. Baird, E. C. Fahmy, with additional contributions by C. McNeil and G. J. Wilson. Fourth edition. Edinburgh, E. & S. Livingstone, 1944. 1208 pages; 511 illustrations. £2 2s. [£2.1]

This book, the collective work of several eminent Scottish obstetricians and gynaecologists, first appeared in 1923, having for its object the closer correlation of obstetrics and gynaecology. The physiology and pathology of pregnancy are discussed in detail and the book deals in a practical manner with the management of normal and complicated labour, the puerperium, antenatal supervision, the disorders of early infancy, and the gynaecological problems met with in general practice; the major gynaecological operations are briefly described. The fourth edition contains 59 chapters, grouped under the following sectional headings: (i) anatomy and physiology; (ii) normal pregnancy; (iii) pathology of pregnancy; (iv) normal labour; (v) abnormal labour; (vi) the puerperium; (vii) the infant in the first month; (viii) obstetric operations; (ix) maternal mortality; (x) gynaecology; (xi) gynaecological operations; (xii) radiology.

The chapter on analgesia and anaesthesia contains important alterations, and additional matter has been incorporated in the chapter dealing with the health, nutrition and disorders of the newly born infant. The section on sterility includes for the first time notes on artificial insemination and birth control. The remaining sections of the book bear evidence of careful revision. Some fine coloured plates are included among the large number of illustrations, and an excellent index completes the work.

387/46

SURGERY OF MODERN WARFARE

edited by Hamilton Bailey. Sub-editor for medicine, C. Allan Birch. Third edition. Edinburgh, E. & S. Livingstone, 1944. Part IV: 210 pages; 244 illustrations. 15s. [£0.75]. Part V: 180 pages; 115 illustrations. 15s. [£0.75]

The third edition of *Surgery of Modern Warfare* is being published in six parts, each bound in cloth. Seventy-seven contributors are collaborating in the work, under the editorship of Hamilton Bailey.

Part IV considers wounds of bones and joints, wounds of the hand and foot, wounds of tendons and peripheral nerve injuries, wounds and injuries of the spine, wounds of the head and neck.

Part V concludes the section on head and neck wounds, and deals with otorhinolaryngology in relation to war injuries, wounds of the eye and orbit, wounds of the trunk. All these subjects are discussed by well-known authorities with practical experience of modern war surgery. As in previous editions, the work is very well produced and lavishly illustrated with colour and half-tone plates and with line drawings.

387/47

AN INTRODUCTION TO PHARMACOLOGY AND THERAPEUTICS

by J. A. Gunn. Seventh edition. Oxford University Press: London, Humphrey Milford, 1944. 268 pages. 7s. 6d. [£0.375]

This was written originally to serve as a background for the student attending lectures on pharmacology and therapeutics, but

now, in its seventh edition, it has become recognised as one of the most useful short surveys of these subjects available. The author is Professor of Therapeutics and Director of the *Nuffield Institute for Medical Research*, Oxford. The present edition has been revised in accordance with the permanent changes made in the British and American pharmacopœia during the last few years, and with the recent advances in pharmacology and therapeutics. Chapter headings: (i) introduction; origin, action, preparation and administration of drugs; (ii) water and salts; (iii) kations of the blood; (iv) drugs acting on the alimentary canal; (v) heavy metals; (vi) metalloids; (vii-ix) drugs acting on the central nervous system; (x) drugs acting on sensory nerves; (xi-xii) drugs acting at efferent nerve-ends; (xiii) drugs which act directly on involuntary muscle; (xiv) drugs acting on heart-muscle; (xv) drugs acting on the respiratory system; (xvi) drugs which influence metabolism; (xvii) phenol and allied aromatic compounds; (xviii) central antipyretics and analgesics; (xix) drugs used in bacterial infections; (xx) drugs used in trypanosomiasis and protozoal infections; (xxi) drugs used in worm infections. There is a good index.

387/48

POLYGLOT GLOSSARY OF COMMUNICABLE DISEASES

Contribution to the International Nomenclature of Diseases, *Bulletin of the Health Organisation, League of Nations*, 10, 201-556, 1943/44. Geneva. [London, Allen & Unwin.] 4s. [£0.2]

This glossary has been compiled by Dr. Yves Biraud, Head of the Service of Epidemiological Intelligence and Public Health Statistics of the League of Nations. There are four parts: (i) Description and method of use of the glossary. (ii) List of names of communicable diseases in the various languages following the classification adopted in the detailed International List of 1938. In this list, the description according to the International List (in French) is followed by the descriptions in Latin, German, English, Bulgarian, Danish and Norwegian, Spanish, Estonian, Finnish, French, Greek, Hungarian, Icelandic, Italian, Latvian, Lithuanian, Dutch, Polish, Portuguese, Rumanian, Russian, Serbo-Croatian, Swedish, Czech and Turkish. (iii) Alphabetical index. (iv) Tables of correspondence between the items of the detailed and abridged International Lists of Causes of Death of 1938 and 1929.

387/49

A PROVISIONAL CLASSIFICATION OF DISEASES AND INJURIES FOR USE IN COMPILING MORBIDITY STATISTICS

Medical Research Council, Special Report Series No. 248. London, H.M. Stationery Office, 1944. 168 pages. 3s. [£0.15]

This report has been prepared by the Committee on Hospital Morbidity Statistics of the *Medical Research Council*. The Committee was formed in response to a request from the Ministry of Health to the *Council* to advise on a standardised classification of disease for use in civilian and military hospitals and with reference to the official Medical History of the War.

The classification adopted in this report is provisional, but has been adopted by the Ministries of Health and of Pensions. Equivalent code numbers of the International List of Causes of Death and the Diagnosis Code of the United States Public Health Service are given. The report is divided into the following sections: (i) introduction and coding rules; (ii) classification of diseases and injuries; (iii) tabular list arranged in the serial order of the International List of Causes of Death (fifth revision, 1938), with the applicable morbidity classification code number attached; (iv) therapeutic classification; (v) classification of occupations.

It is anticipated that modifications will be necessary as a result of practice trial of the system, and users are invited to send criticisms and suggestions to the Secretary of the Committee, Dr. A. H. T. Robb-Smith.

387/50

INDEX TO THE MANUAL OF THE INTERNATIONAL LIST OF CAUSES OF DEATH

(5th Revision, 1938)

For use with the Medical Research Council's Provisional Classification of Diseases and Injuries, 1943 (Special Report Series, No. 248). London, H.M. Stationery Office, 1944. 92 pages. 2s. [£0.1]

387/51

THE USE OF PENICILLIN IN TREATING WAR WOUNDS

Medical Research Council War Memorandum No. 12. London, H.M. Stationery Office, 1944. 16 pages. 3d. [£0.0125]

This memorandum has been prepared by the Penicillin Clinical Trials Committee of the *Medical Research Council*. It provides

guidance in the use of penicillin in the treatment of wounds and in the laboratory control of treatment, and the provisional instructions are based largely on reports made by Professor H. W. Florey and Brigadier H. Cairns as a result of a visit to North Africa. There are summaries of the properties of penicillin and of susceptible and insusceptible organisms, of methods of dispensing and of administration, and of the uses of penicillin in (a) surface wounds and burns, (b) soft tissue wounds, (c) gas gangrene, (d) compound fractures, (e) wounds of the chest, (f) head injuries, (g) wounds of the eye, (h) wounds of the abdomen. Some of the possible reasons for disappointing results are given in "Remarks on Failures of Technique." "Laboratory Procedures" are reviewed and there is a select bibliography on penicillin.

The recommendations in the memorandum are not intended to have any finality but are an authoritative summary of conclusions reached as a result of experience before the Allied invasion of France.

387/52

REPORT ON MEDICAL EDUCATION

by the Planning Committee, Royal College of Physicians of London. Published by the Royal College of Physicians, Pall Mall East, London, S.W.1, 1944. 42 pages. Gratis

Medical education in Britain has, with some exceptions, developed from a system of apprenticeship and of private medical schools attached to large hospitals and has been largely independent of the universities. Emphasis has been more on practical training than on theory. This report is concerned specifically with reforms in the British system. The main conclusions are that the selection of medical students should be more discriminating and that the financial barrier to the study of medicine should be lowered. Changes in the curriculum are required. These are mainly in the direction of sacrifice of detail in the interest of a greater understanding of principles and the scientific method. In particular, it is recommended that far less time should be given in the pre-clinical period to topographical anatomy. There should be greater co-ordination between pre-clinical and clinical studies, which are at present sharply differentiated. Teachers of clinical medicine should receive sufficient remuneration and secretarial and technical assistance to enable them to devote full attention to their duties.

It is recommended that a compulsory paid internship of one year should be added to the curriculum, and that there should be two final examinations instead of one. The first would confer a licence to practice under supervision in hospital, and the second, which would be taken at the end of the one-year term of residence at a hospital, would confer the right to practise independently.

Although many of these recommendations will not be relevant to conditions in other countries, the report should be of interest to all who are concerned with medical education.

387/53

FOOD POISONING

Its Nature, History and Causation; Measures for its Prevention and Control

by E. B. Dewberry. London, Leonard Hill, 1943. 186 pages; 44 illustrations. 15s. [£0.75]

Although from time immemorial food has been recognized as a cause of disease, it is only comparatively recently that work on ptomaines and the discovery of pathogenic bacteria in food have shown that it has little or nothing to do with the illness except to act as a carrier.

This book gives a full account of bacterial food poisoning, contamination of food by metals, and poisonous plants, fungi, fish and shell-fish. Historical prefaces to parts I and III trace the development of our knowledge concerning food poisoning, from the early investigations to the more important bacteriological discoveries and the most recent studies. Wide use has been made of public health reports and other important publications, and comprehensive lists of references are appended to each chapter for the use of those wishing to consult the original sources.

Chapter headings: Part I: (i) introduction, (ii) historical, (iii) bacterial food poisoning, (iv) seasonal prevalence of bacterial food poisoning, (v) kinds of food that act as vehicles of infection, (vi) possible sources and modes of infection, (vii) prevention and control of bacterial food poisoning; Part II: (viii) contamination of foods by poisonous metals, (ix) poisonous plants, edible and poisonous fungi, (x) poisonous fish and shell-fish, (xi) food allergy; Part III, Botulism; (xii) historical, (xiii) symptomatology, differential diagnosis, (xiv) causation, bacteriology, (xv) spores of *Cl. botulinum*, (xvi) toxin of *Cl. botulinum*, (xvii) kinds of food associated with outbreaks of botulism, (xviii) illustrative outbreaks, (xix) prevention and control. Two appendixes describe (i) decontamination of foods contaminated by poisonous gases in war and (ii) steps to be taken by medical officers of health in suspected cases of food poisoning. The half-tone illustrations include portraits of outstanding personalities in this branch of public health, and full author and subject indexes are provided.

GUIDE TO THE JOURNALS

Annals of Eugenics

12 : May 1944

- An analysis of the blood-group composition of a population in Northern Ireland. (E. W. Hart) 89-101
The experimental modification of dominance in Danforth's short-tailed mutant mice. (R. A. Fisher & S. B. Holt) 102-120
A demographic study of a psychopathic population. (E. Slater) 121-137
Sampling moments of moments for a finite population. (J. O. Irwin & M. G. Kendall) 138-142
The numbers of publications written by biologists. (C. B. Williams) 143-146

Archives of Disease in Childhood

19 : March 1944

- Erythroblastosis foetalis. (J. R. Gilmour) 1-25
A scheme for the prevention of cross infection in children's wards. (N. M. Jacoby) 26-28
Encephalo-meningitis due to pneumococcus type 1. (M. J. Wilmers) 29-31
Familial spastic paresis with strabismus. (M. P. Crowe) 32-33
Dolichocolon and Hirschsprung's disease. (A. Moncrieff & T. V. Crichtlow) 34-36

British Heart Journal

6 : April 1944

- Paroxysmal heart block and ventricular standstill. (J. S. Lawrence & G. W. Forbes) 53-60
Heart block with aneurysm of the aortic sinus. (P. F. Duras) 61-65
Stokes-Adams attacks in a child. (V. S. Stern) 66-68
Complete heart block. (M. Campbell) 69-92
A rare case of complete heart block. (K. Saracoglu) 93-95
The care of rheumatic children: Report by the Cardiac Society and British Paediatric Association. 99-102
Social and economic conditions and the incidence of rheumatic heart disease. (G. H. Daniel) 103-104
Unusual electrocardiogram in dextrocardia. (J. M. Holford) 105-106
Auriculo-ventricular rhythm. (R. A. Miller) 107-113

British Journal of Children's Diseases

41 : April-June 1944

- Meningitis in children refractory to sulphonamides. (R. Gross-Heister & E. Davis) 31-34
Pathogenesis and clinical symptoms of tuberculous meningitis. (S. Engel) 34-38

British Journal of Dermatology and Syphilis

56 : March-April 1944

- The role of the sulphonamides in dermatology. (R. StA. Heathcote) 59-68
Sulphonamides in dermatology. (D. M. Pillsbury) 68-80
Seborrhoeic skin eruptions. (J. A. Scott) 80-91
A method of testing absorption from various ointment bases. (J. Rae) 92-94

British Journal of Industrial Medicine

1 : April 1944

- The training of the industrial nurse. (A. J. Amor & C. Sykes) 81-89
Design of dressing stations and control of wound infection. (W. Gissane, A. A. Miles & R. E. O. Williams) 90-98
First-aid treatment of burns and scalds. (L. Colebrook, T. Gibson & J. P. Todd) 99-105
Burns of the hand. (P. H. Jayes) 106-109
Prevention and control of cutting-oil dermatitis. (E. Collier) 110-113
New aspects of nutrition. (J. R. Marrack) 114-122
Medical service in industry in the U.S.S.R. (A. Letavet) 123-124

British Journal of Ophthalmology

28 : June 1944

- The Eye Department in a Middle East general hospital. (H. B. Stallard) 261-275
A simple method for the early diagnosis of abnormalities of the pupillary reaction. (H. J. Stern) 275-276
A granulation tumour of the conjunctiva. (J. D. J. Freeman) 277-278
The genetics of retinoblastoma. (A. D. Griffith & A. Sorsby) 279-293
An encapsulated orbital melanoma. (J. Foster) 293-296
Removal of a non-magnetic foreign body from the vitreous. (V. O'Hear-Cussen) 296-298

British Journal of Radiology

17 : June 1944

- The diagnosis and treatment of lung abscess. Symposium. (T. H. Sellors, L. G. Blair & L. E. Houghton) 165-176
Energy absorption—II. Part II—Integral dose when the whole body is irradiated. (W. V. Mayneord & J. R. Clarkson) 177-182
A case of peptic ulcer on the greater curvature of the stomach. (A. Preiss) 182-184
Cancer of the lip. (S. J. Douglas) 185-189
A geometrical method of dose-finding for radium sources: with special reference to the treatment of carcinoma cervix uteri. (B. Sandler & E. M. Ungar) 190-196

British Journal of Venereal Diseases

20 : June 1944

- Sulphonamides in gonorrhoea. (W. K. Fitch) 49-55
Specific reactions occurring in the treatment of lymphogranuloma venereum with immune animal sera. (F. Sager) 55-60
Prevention of congenital syphilis—1. (N. I. Wartie) 61-65
Prevention of congenital syphilis—2. (D. Nabarro) 65-69
The trend of antisyphilitic treatment. (D. Erskine) 73-77
Comparison of the Laugher reaction for syphilis with the Wassermann and Kahn reactions. (C. R. Lane) 78-81

British Medical Journal

1 : 6/5/44

- The control of dust-borne streptococcal infection in measles wards. (J. Wright, R. Cruickshank & W. Gunn) 611-614
A new technique for the application of dust-laying oils to hospital bed-clothes. (F. C. Harwood, J. Powney & C. W. Edwards) 615-616
Oiled floors to control respiratory infection: an army experiment. (P. H. R. Anderson, J. A. Buchanan & J. J. MacPartland) 616-617
The determination of basal metabolism on out-patients. (J. D. Robertson) 617-619
Nutritional oedema in a vegetarian. (J. M. Holmes) 620
Aerial convection from smallpox hospitals. (C. K. Millard) 625-629

1 : 13/5/44

- A national health service: report of the Council of the B.M.A. to the representative body. 643-648
Replies by the Minister of Health to questions put to him by the representative committee. 648-652
Head injuries involving air sinuses. (D. McKenzie) 652-654
Use of crude penicillium filtrate for local treatment. (J. M. Alston) 654-656
Autolysed yeast in the treatment of nutritional macrocytic anaemia. (G. R. Sippe) 656-658
Famine oedema in prisoners of war. (D. S. Stevenson) 658-660
Some impressions of slow starvation in China. (H. T. Laycock) 667-668

1 : 20/5/44

- The course of the death rate from peptic ulcer in Great Britain, 1912-38. (H. Tidy) 677-682
Treatment of gas gangrene. (J. D. MacLennan & M. G. Macfarlane) 683-685
Fracture of the carpal scaphoid. (J. M. Robertson & R. D. Wilkins) 685-687
Epidemic infective hepatitis in Gloucestershire. (J. S. Cookson) 687-689
Experiments on scabies prophylaxis. (K. Mellanby) 689-690
Planning for basic research in ophthalmology. (C. G. K. Sharp) 697-698

1 : 27/5/44

- With the Eighth Army in the field. (C. Donald) 709-714
Sensitivity to liver extract. (J. G. McSorley & L. S. P. Davidson) 714-716
Experimental traumatic shock. (J. Charnley) 716-718
Dicoumarin in the treatment of puerperal thrombosis. (A. Davis & M. Porter) 718-719
Effect of nicotinic acid on post-operative vomiting. (W. W. Mushin & H. M. Wood) 719-720

1 : 3/6/44

- Some problems of infective hepatitis. (L. J. Witts) 739-743
With the Eighth Army in the field—II. (C. Donald) 743-747
Some dangers of sulphonamides in ear infections. (A. R. Dingley) 747-748
Bone-marrow transfusion in infants and children: introducing a specially designed needle. (J. D. Gimson) 748-749
"Cellophane" for the treatment of burns. (J. Farr) 749-750
Symptomless enlargement of the oesophagus. (J. L. D'Silva) 750-751
Research and general practice: the end-results of treatment. (C. E. S. Flemming) 759-760

1 : 10/6/44

- Analysis of shock. (V. H. Moon) 773-779
Meningitis due to Pittman and non-Pittman strains of *H. influenzae*. (J. Gordon, H. E. de C. Woodcock & K. Zinnemann) 779-781
Sulphonamide allergy. (R. G. Park) 781-782
Treatment of pulp infection of the fingers in the field. (T. Denness) 782-783
Early operation for Volkmann's ischaemic contracture. (G. A. Pollock) 783

1 : 17/6/44

- Control of scabies by use of soap impregnated with tetra-ethylthiuram monosulphide ("Tetmosol"). (R. M. Gordon, T. H. Davey, K. Unsworth, F. F. Hellier, S. C. Parry & J. R. B. Alexander) 803-806
The carrier state in Sonne dysentery. (J. G. Hailwood) 806-807
An analysis of Colles's fracture. (S. C. Rogers) 807-809
An outbreak of puerperal sepsis due to a single type of haemolytic streptococcus: its investigation and remedy. (M. Kenny & M. Barber) 809-811
Narco-analysis with nitrous oxide. (C. H. Rogerson) 811-812
Medicine in free China. (W. Penfield) 821-822

1 : 24/6/44

- An experimental study of methods of artificial respiration. (A. Hemingway & E. Neil) 833-836
The improved dentition of 5-year-old London school-children: a comparison between 1943 and 1929. (M. Mellanby & H. Coumoulos) 837-840
Poliomyelitis in British and American troops in the Middle East: the isolation of virus from human faeces. (J. R. Paul, W. B. Havens & C. E. van Rooyen) 841-843
Sympathectomy and sterility. (N. C. Lake) 843
March haemoglobinuria. (M. Makin) 844

2 : 1/7/44

- Penicillin in battle casualties. (J. S. Jeffrey & S. Thomson) 1-4
Early diagnosis of peripheral nerve injuries in battle casualties. (W. R. Russell & A. B. Harrington) 4-8
Acute haemolytic anaemia: report of a case presenting hitherto unreported features. (J. P. Currie) 8-10
Typhus fever in Great Britain. (A. P. Agnew & W. B. Kyles) 10-11
Tetanus after head injury in an immunized subject. (W. Lewin) 11-12

Edinburgh Medical Journal

51 : March 1944

- Cancer and chronic disease. (J. Eason) 113-123
Aeration of fluid culture media: supplementary observations. (R. Devignat) 124-130
A pathologist looks at ischaemia. (W. Blackwood) 131-143
The Court of Contributors, Royal Infirmary of Edinburgh. (D. Robertson) 144-151
The sterno-mastoid sign. (A. W. Branwood) 152-156

51 : April 1944

- Intersigmoid hernia: report of case and review of the literature. (H. D. Wilson) 161-165
Military surgery in geographical perspective: a Libyan exercise in surgical strategy and tactics. (I. Aird) 166-183
The aetiology, prophylaxis and treatment of cholecystitis and cholelithiasis. (L. S. P. Davidson) 184-200
Acute schizophreniform psychosis in childhood: report of a case. (L. F. W. Endicott) 201-204

Journal of Endocrinology

3 : May 1944

- On staining the basophil cells of the human hypophysis, with special reference to the abnormal basophil cells of Cushing's syndrome. (N. G. B. McLetchie) 323-331
The pituitary basophilism syndrome of Harvey Cushing. (N. G. B. McLetchie) 332-346
Carcinoma of an adrenocortical rest associated with hypophyseal abnormality. (N. G. B. McLetchie & L. D. W. Scott) 347-355
Disturbances of water balance in the rat on removal of the adrenal medulla. (L. Stein & E. Wertheimer) 356-360
The nature of the hyperostosis observed in the long bones of rats treated with excessive doses of oestradiol benzoate. (H. N. Lippman & J. B. de C. M. Saunders) 370-383
The production of ovulation in the immature rat. (I. W. Rowlands) 384-391

Additional studies of the extrathyroidal metabolism of iodine. (A. Chapman, G. M. Higgins & F. C. Mann) 392-396
 Ateleiotic dwarfism with normal sexual function: a result of hypopituitarism. (T. F. Hewer) 397-400
 Observations on the œstrogenic potency of stilbœstrol in the guinea-pig. (P. Bacsich & G. M. Wyburn) 401-405

Journal of Obstetrics & Gynaecology

51: June 1944

The effect of posterior lobe pituitary gland fractions on the intact human uterus. (C. Moir) 181-197
 The anæmias of pregnancy: a report on the hæmatological study of 48 cases of pregnancy with a review of the literature. (G. A. Elliott) 198-224
 A human ovum nine to ten days old. (F. Davies & H. E. Harding) 225-230
 Leukæmia and pregnancy. (A. Hochman) 231-239
 A consideration of the White Paper "A National Health Service" in so far as it affects maternity and child welfare services. (D. Baird) 240-246
 Oxytocic drugs and their use. (C. Moir) 247-256

Journal of Pathology and Bacteriology

56: April 1944

The pinealoma: its relationship to teratoma. (D. S. Russell) 145-150
 The sources of blood platelets and their adhesiveness in experimental thrombocytosis. (H. P. Wright) 151-159
 Spontaneous folliculosis of the conjunctiva in grivet and vervet monkeys (*Lasiopyga griseoviridis* syn. *Cercopithecus aethiops* and *L. pygerythra* syn. *C. pygerythra*) and the susceptibility of the grivet to trachoma virus. (J. O. W. Bland) 161-171
 The filtration of *Mycobacterium tuberculosis* and *Mycobacterium stercoris* through gradocol membranes. (M. A. Soltys & A. Wilson Taylor) 173-180
 A developing factor in experimental blastogenesis. (J. C. Mottram) 181-187
 The anæmia associated with infection. (M. F. Saifi & J. M. Vaughan) 189-197
 The architectural structure of the upper end of the femur in various pathological conditions. (W. Townsley) 199-207
 A chronic human carrier of *B. artrycke* (*Bact. typhi-murium*) treated by cholecystectomy. (H. Burt) 209-215
 Toxic effects of propamidine, with special reference to the treatment of burns. (J. W. Allen, F. Burgess & G. R. Cameron) 217-223
 Diabetogenic and pancreotropic actions of ox anterior pituitary extract in rabbits. (R. F. Ogilvie) 225-235
 The incidence and causes of discrepancies in the results of serological tests for syphilis. (F. M. Berger & P. L. Sutherland) 237-246

Journal of Physiology

103: June 1944

Effect of age upon dark adaptation. (G. W. Robertson & J. Yudkin) 1-8
 The action of vitamin D upon the incisor teeth of rats consuming diets with a high or low Ca:P ratio. (J. T. Irving) 9-26
 The nature of synaptic transmission in a sympathetic ganglion. (J. C. Eccles) 27-54
 The action of adrenaline on transmission in the superior cervical ganglion (E. Bülbring) 55-67
 The pressor bases of normal urine. (M. F. Lockett) 68-92
 Action of acetylcholine, atropine and eserine on the central nervous system of the decerebrate cat. (I. Calma & S. Wright) 93-102
 Stimulus intensity in relation to excitation and pre- and post-excitatory inhibition in isolated elements of mammalian retina. (R. Granit) 103-118
 The role of the peripheral stump in the control of fibre diameter in regenerating nerves. (F. K. Sanders & J. Z. Young) 119-136

Lancet

1: 6/5/44

State of men severely wounded in battle. (W. C. Wilson) 587-591
 Sulphathiazole-proflavine powder in wounds. (J. McIntosh, F. R. Selbie, with clinical reports by R. V. Hudson, D. H. Patey, T. Parkes, H. L. McMullen & G. C. L. Pile) 591-593
 Sulphathiazole-proflavine powder in war wounds. (G. Y. Feggetter) 593-594
 Control of sepsis in a hospital in North Africa: with observations on sulphathiazole-proflavine powder in surgical wounds. (P. B. Ascroft) 594-595
 Carcinoma of the prostate treated with stilbœstrol. (J. D. Fergusson) 595-597
 Pentothal anæsthesia in bronchoscopy. (L. Fatti & H. J. V. Morton) 597-598
 Delayed rupture of the spleen. (H. Bell & G. H. Steele) 598

1: 13/5/44

Reflections upon reform in medical education. I. Present state and needs. (T. Lewis) 619-621
 Injuries to the main bile-ducts. (G. G. Turner) 621-622
 Homologous serum jaundice: transmission experiments with human volunteers. (F. O. MacCallum & D. J. Bauer) 622-627
 Marfanil and marfanil prontosilbin. (G. A. G. Mitchell, W. S. Rees & C. N. Robinson) 627-629
 Two cases of leprosy in London. (H. Haber) 629-630
 Nomenclature of malnutrition. (L. Nicholls) 630
 Pharmacology of thiourea. (D. Campbell, F. W. Landgrebe & T. N. Morgan) 630-632
 Prostheses for children. (A. W. J. Craft) 639-642

1: 20/5/44

Reflections upon reform in medical education: II. Principal educational reforms. (T. Lewis) 649-651
 War surgery of the extremities in the light of recent experience. (J. Trueta) 651-653
 Case finding by mass radiography: a report on 500 selected cases. (A. Kahan & H. G. Close) 653-654

Pneumococcal meningitis treated with penicillin. (H. Cairns, E. S. Duthie, W. S. Lewin & H. V. Smith) 655-659
 The fractured femoral shaft: new approach to the problem. (G. R. Fisk) 659-661

1: 27/5/44

Gunshot wounds of the knee-joint. (St. J. D. Buxton) 681-684
 Reflections upon reform in medical education. III. Medical research within the teaching school. (T. Lewis) 685-687
 Effect of vitamin-C deficiency on experimental wounds: tensile strength and histology. (G. H. Bourne) 688-691
 Pruritus ani: a practical approach. (A. J. Cantor) 692
 Tissue culture of malaria parasites (*Plasmodium gallinaceum*). (F. Hawking) 693-694

1: 3/6/44

Education for health. (J. A. Ryle) 713-715
 Retrobulbar optic neuritis: a pathognomonic sign. (R. A. Greeves) 715
 Wounds of the bladder. (J. G. Sandrey & R. A. Mogg) 716-720
 Stomatitis due to riboflavin deficiency. (H. E. Jones, T. G. Armstrong, H. F. Green & V. Chadwick) 720-723
 Early movement in the treatment of closed fractures. (B. H. Burns & R. H. Young) 723-725

1: 10/6/44

Management of minimal pulmonary tuberculosis disclosed by fluorography. (W. D. W. Brooks) 745-748
 Comminuted fractures of mandible: a report on 25 consecutive cases from a Plastic and Jaw Unit EMS. (J. B. Cuthbert) 748-750
 The human factor in military malaria control. (R. R. Bomford) 750-753
 Angular conjunctivitis treated with propamidine. (F. C. O. Valentine & A. M. Edwards) 753-754
 Ankylosing spondylitis. (E. Fletcher) 754-756
 Facial palsy in closed head injuries: the prognosis. (J. W. A. Turner) 756-757
 Pyreto-electric shock therapy in schizophrenia. (J. Fuster) 757-759
 Adsorption of acridines by gauze. (A. Albert & W. S. Gledhill) 759-760

1: 17/6/44

Substances chemotherapeutically active against typhus rickettsiæ. (C. H. Andrewes, H. King, M. van den Ende & J. Walker) 777-781
 Wounds of the neck and larynx. (R. S. Lewis) 781-784
 Comparative effects of sulphonamide drugs in mild bacillary dysentery. (J. G. Scadding) 784-786
 Treatment of fractures of the femoral and tibial shafts in the same limb. (V. H. Ellis, H. H. Langston & J. S. Ellis) 786-787
 Further observations on the use of cetavlon (Ctab) in surgery. (R. E. O. Williams, B. Clayton-Cooper, H. C. Faulkner & H. E. Thomas) 787-788
 Blast injury: Non-fatal case with neurological signs. (O. Garai) 788-789
 Dislocation of sesamoid of hallux. (G. M. Müller) 789
 Abscess in the thyroid gland: Report on two cases. (F. E. Stock) 789-790
 Medicine and nursing in Ethiopia. (R. Young) 797-798

1: 24/6/44

Epidemiology of wound infection. (A. A. Miles) 809-814
 Hepatitis following injection of mumps convalescent plasma: I. Use of plasma in the mumps epidemic. (P. B. Beeson, G. Chesney, & A. M. McFarlan) 814-815
 Hepatitis following injection of mumps convalescent plasma: II. Epidemiology of the hepatitis. (A. M. McFarlan & G. Chesney) 816-817
 Hepatitis following injection of mumps convalescent plasma: III. Clinical and laboratory study. (W. L. Hawley, A. M. McFarlan & A. J. Steigman, with liver biopsy studies by J. McMichael & J. H. Dible) 818-821
 Impaction of a prostatic stone in a urethral stricture. (J. B. Kinmonth & J. L. Pinniger) 821-822
 Pentothal sodium in North Africa: 2,500 administrations at a base hospital. (E. S. Curtiss) 822-823
 Gunshot wound of the colon: recovery without immediate operation. (W. W. Wilson) 824
 Industrial neuroses: analysis of 100 cases. (T. M. Ling) 830-832

2: 1/7/44

Teaching and practice in preventive medicine. (J. M. Mackintosh) 1-5
 Retroperitoneal gas. (G. E. Parker) 5-7
 Prevention of jaundice resulting from antisyphilitic treatment. (M. H. Salaman, A. J. King, D. I. Williams & C. S. Nicol) 7-8
 Epidemiology of infective hepatitis. (H. L. Sheehan) 8-11
 Evacuation of the fractured femur: the Tobruk plaster and other methods used in the Middle East. (E. A. Jack) 11-13

Quarterly Journal of Pharmacy and Pharmacology

17: January-March 1944

A comparison of some of the ergot alkaloids. Part II. Action on temperature regulation in the mouse and the rabbit. (A. C. White) 1-7
 A comparison of the biological and chemical assays of *Atropa Belladonna* and *Atropa acuminata*. (J. A. Gunn) 7-18
 The cardiovascular actions of some amines related to adrenaline. (J. D. P. Graham) 19-29
 The assay of pamaquin. (C. W. Ballard & J. S. Pierce) 30-38

Tubercle

25: January-February 1944

B.C.G. vaccination in Norway. (O. G. Hansen) 1-6
 Respiratory folk-lore. (J. D. Rolleston) 7-12

CORRIGENDA: VOL. 2

Nos. 3-4

BMB 292

On page 60, column 2, line 8, for Council read Council.

In the References, for MacGregor, I. N., read MacGregor, T. N.; for Carmichael, E. H., read Carmichael, E. A.; for Fraser, S. R., read Fraser, F. R.

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In line 11, for (Craig, 1933) read (Craig, 1936).

BMB 337

In line 1, for or systemic read of systemic.

No. 5

On page 94, line 15, for material read maternal

BRITISH MEDICAL BULLETIN

Vol. 2 (1944) No. 7

PERIPHERAL VESSELS

SPECIAL CONTRIBUTIONS

PERIPHERAL VASCULAR DISORDERS	
by Professor J. R. Learmonth	136
LOW TEMPERATURE INJURY : PATHOLOGY	
by Dr. W. Blackwood	138
LOW TEMPERATURE INJURY : CLINICAL FEATURES, PREVENTION, TREATMENT	
by Dr. R. L. Richards	141
TREATMENT OF ARTERIAL INJURIES	
by Mr. B. C. Maybury	142
TRAUMATIC ARTERIAL SPASM	
by Mr. S. M. Cohen	144
PHOTOGRAPHS ILLUSTRATING THE PATHOLOGY OF IMMERSION FOOT	139

REVIEW OF SELECTED PAPERS

Peripheral Vascular Disorders	
Discussion on Immersion Injuries and Vasomotor Disorders in Wartime	146
Injury from Exposure to Low Temperature	
Swelling of Human Limbs on Immersion in Cold Water	147
Immersion Foot and Immersion Hand : Preliminary Observations	147
Animal Experiments on Immersion in Cold Water	147
Immersion Foot and Immersion Hand : Further Observations	148
Ætiology of Immersion Foot	148
Pathology of Immersion Foot	149
Immediate Vascular Changes in True Frostbite	149
Immersion Foot and Frostbite after Shipwreck	149
Instructions to Mariners on Immersion Foot and Frostbite	150
Treatment by Low Temperature	
Cold in the Treatment of Damage due to Cold	150
Treatment of Immersion Foot by Dry Cooling	151
Some Uses for Dry Cold Therapy	151
Nervous Control of Peripheral Circulation	
Mechanism of Vasomotor Reflexes on Stimulation of Sensory Nerves	152
Spinal Origin of Vasoconstrictor Fibres to Human Arm	152
Vasomotor Disturbances after Peripheral Nerve Injuries	152
Reflex Vasodilatation in Surgery	153
Sympathectomy in the Treatment of Cryopathies	154
Ischæmia	
Localised Arterial Thrombosis of Indeterminate Origin	154
Pathology of Ischæmia	154
Volkmann's Ischæmic Contracture	155
Traumatic Ischæmia in the Forearm and Leg	155
Volkmann's Ischæmia of the Leg	155

BOOKS, MEMORANDA, REPORTS ... 156

GUIDE TO THE JOURNALS ... 158

This number deals principally with peripheral vascular disorders which have proved to be of special importance in wartime. Professor J. R. Learmonth, who contributes the introductory article, has occupied the Chair of Surgery in the University of Edinburgh since September 1939. He was previously Regius Professor of Surgery in the University of Aberdeen. He has charge of a Nerve Injuries Unit and Peripheral Vascular Unit in an Emergency Medical Service hospital under the Department of Health for Scotland, where many patients suffering from peripheral vascular disorders have been concentrated during the war.

Dr. William Blackwood has been Pathologist to the Scottish Mental Hospitals Laboratory, the Royal Infirmary, Edinburgh, and Honorary Lecturer in Neuropathology in the University of Edinburgh since 1939. Work on immersion foot arose out of these contacts, and from a meeting with Surgeon Commander C. C. Ungley, after he had sent a portion of nerve for biopsy to Dr. Blackwood's predecessor, Squadron-Leader A. C. P. Campbell.

Dr. R. L. Richards, a graduate of Aberdeen University, has since the summer of 1940 been assistant at a Scottish Nerve Injuries Unit in an Emergency Hospital under the Department of Health for Scotland. He has been making a special study of the vasomotor disorders which result from injuries of peripheral nerves. Work on immersion foot has been carried out in collaboration with Surgeon Commander C. C. Ungley at a naval hospital in Scotland and at the Nerve Injuries Unit directed by Professor Learmonth.

Mr. B. C. Maybury is Surgeon to St. Thomas's Hospital, London, where he was earlier a pupil of Sir George Makins and Sir Cuthbert Wallace—two pioneers of military surgery. Mr. Maybury was for nearly three years during the war of 1914–18 a surgical specialist at a Casualty Clearing Station, and also spent a short time at a Base Hospital. He has had considerable personal experience of arterial injuries and has long had a special interest in this subject.

Mr. S. M. Cohen is a South African surgeon who joined the British Emergency Medical Service at the outbreak of war, and has thus gained experience of the treatment of war casualties. He has made a special study of traumatic arterial spasm, and chose this as the subject for his lecture on election in 1942 as Hunterian Professor of the Royal College of Surgeons of England.

Professor Learmonth, Mr. Cohen, and Mr. Maybury are members of a Subcommittee on Vascular Injuries which was constituted early in 1944 by the War Wounds Committee of the Medical Research Council.

In the planning of this number of the *Bulletin* Professor Learmonth has given much personal advice and assistance. In addition, he and his Edinburgh colleagues, Dr. Blackwood and Dr. Richards, have contributed many of the reviews of selected papers.

SPECIAL CONTRIBUTIONS

389

PERIPHERAL VASCULAR DISORDERS

J. R. LEARMONTH, CH.M., F.R.C.S.ED.

The pathological conditions dealt with in this issue of the *Bulletin* have this in common, that in all the possibility of ischæmia is present. This may arise without any breach of the arterial tree by external forces; on the other hand, when an artery is wounded, in addition to the complete or partial interruption of the conduit supplying blood to a part, there will be hæmorrhage, internal, external, or both, and thus any tendency to ischæmia as a result of the loss of one (or more) of the transmitting channels may be accentuated by a reduction in the total volume of the circulating blood. These considerations suggest the following clinical classification of the affections which may produce ischæmia:

A. Resulting from Injury

1. Contusions of arteries : (a) with thrombosis
(b) without thrombosis
2. Arterial spasm : (a) after open injuries (neighbourhood gunshot wounds)
(b) after closed injuries (fractures, crush injuries)
3. Wounds of arteries : (a) complete
(b) partial
4. Arterial hæmatomata or "false" aneurysms
5. Arteriovenous fistulæ
6. Traumatic arteritis
7. Traumatic venous thrombosis (or venous spasm)
8. After division of peripheral nerves

B. Occurring in Organic Vascular Disease

1. Syphilitic arteritis
2. Arteriosclerosis
3. Diabetic arteritis
4. Thrombo-angiitis obliterans

C. From Local Effects of Cold

1. The Raynaud phenomenon, with or without nutritional changes
2. Immersion foot
3. Frostbite

Some of these conditions are dealt with in detail in individual articles elsewhere in this issue; but it cannot be too strongly emphasised that the rational treatment of all of them depends on attention to two fundamental principles: the control of hæmorrhage when present, and the maintenance of tissue nutrition.

Control of Hæmorrhage

In war surgery the control of bleeding is a problem of far greater magnitude and urgency than in civil surgery; yet it is a curious reflection that in spite of the wealth of material, only one major improvement in this technical matter has

emerged directly from military experience—the reintroduction of the ligature by Paré about the middle of the 16th century. In the first two centuries of the Christian era, both Celsus and Galen employed the ligature. The former divided the bleeding vessel between ligatures placed on each side of the vascular wound; the latter raised the artery on a hook, and, in his own words, "it is safer for the operator to put a double loop round it and to divide between, and let these ligatures be of a material which will not readily decompose. Such a material . . . can be got from the Gaietans, who bring it from the country of the Kelts" [? linen]. Galen also suggested catgut: "If you cannot get this" [linen], "choose the material least liable to decompose . . . such as fine catgut." In mediæval times the cautery and boiling oil were preferred to the ligature, until in 1552 Paré reintroduced it, after catching the bleeding parts in a crude forceps. Thereafter the ligature kept its place in operative surgery, although suppuration and consequent secondary hæmorrhage compromised its efficacy, and its use was firmly established by John Hunter in 1785, in the treatment of popliteal aneurysm.

It was natural to seek for an absorbable ligature, which would not promote suppuration by acting as a foreign body. In 1814 Physick used untanned buckskin; in 1818 Astley Cooper employed catgut. Crude catgut, as was to be learnt later, contains bacteria; and after numerous surgeons had tried many different kinds of thread, Lister in 1868 returned to catgut, which he sterilised with carbolic acid. In 1881, he produced catgut hardened by chromic acid to resist absorption for some time, a method of preparation to which Macewen also contributed. Sterilised and hardened catgut has remained the most widely used absorbable ligature. With the advent of modern aseptic operative technique, and the practice of sterilising other forms of thread by boiling, many surgical schools have returned to the unabsorbable ligature of silk, linen or cotton, particularly in aseptic cases.

The general use of the ligature brought with it the need for some method of isolating and temporarily occluding bleeding vessels, and the crude pincers of Paré paved the way for the artery forceps, originally designed by Spencer Wells in 1872, and subsequently modified in ways too numerous to mention, according to the purposes to which it was to be put and the preferences of individual surgeons. So, too, the tourniquet has been modified to meet the needs and gentler methods of modern surgery, although for "first-aid" it persists in its primitive form—introduced by Morel in 1674—of a band of cloth tightened by turning a stick. However useful the tourniquet may be in an emergency, it is to be regarded as a purely temporary substitute for more exact methods.

The local repair of wounds of blood vessels was evolved from the experimental work of Carrel & Guthrie, 1905, from which emerged techniques for the closure of wounds of vessels, and later for the restoration of vascular continuity by axial anastomosis. These methods also opened up the possibility of conservative treatment of arteriovenous fistulae. Their applicability in war surgery is limited because they are available only in favourable conditions including both absence of infection from the wound and proper operative facilities.

Maintenance of Tissue Nutrition

In contrast with the lack of any revolutionary advance in technical methods of controlling bleeding, much more progress has been made in solving the diverse problems of maintenance of tissue nutrition: these advances may be considered in turn.

i. *Restoration of blood volume*: Inadequate circulation resulting from gross reduction in the volume of circulating blood has been dealt with by the perfection of techniques for infusing blood or blood-products.

In Britain the scientific investigation of the possibilities of transfusion dates from the work of the great architect Sir Christopher Wren in 1657, and soon engaged the attention of the newly formed (1661) Royal Society. For two and a half centuries sporadic attempts were made to utilise clinically a procedure at once attractive and somewhat dramatic; but technical difficulties, and the violent and sometimes fatal reactions which followed the transfusion of either animal or human blood, set a limit to its justifiable use until the beginning of the 20th century, when the explanation of at least some of the reactions after transfusion evolved from the discovery of isoagglutination, and the subsequent reduction of human blood into groups (Landsteiner, 1900, 1901; Janský, 1907; Moss, 1910) which provided a basis for the choice of a compatible donor. For some time thereafter, direct transfusion, or transfusion from a vessel coated with paraffin wax (Kimpton & Brown, 1913) were used; but these methods, the former inaccurate, the latter involved, were soon displaced by the discovery (Agote, 1915; Lewisohn, 1915) that sodium citrate was an effective and non-toxic anti-coagulant, and on November 14th, 1914, the first transfusion by this method—so soon to be of cardinal therapeutic importance in the war of 1914–1918—was performed by Agote of Buenos Aires. In the years after the war, transfusion of blood rapidly extended its proven value, and ultimately supplies of donors were organised throughout Britain on a voluntary basis. About 1936 American workers found that it was possible to store citrated blood in blood-banks; and when in 1938 it became clear that large amounts of blood might be needed for casualties, the *Medical Research Council* undertook the establishment of blood supply depots around London, and has since supported and co-ordinated clinical and research work on transfusion in Britain. In Scotland the Department of Health sponsored the foundation of the Scottish National Blood Transfusion Association to co-ordinate and extend transfusion work in Scotland; in England the Ministry of Health, by direct action, organised transfusion services throughout the provinces. A similar "bank" was also set up by the Army Transfusion Service.

The discovery that plasma could be used to restore blood volume was not long delayed; the value of blood-banks was greatly enhanced, for plasma keeps much longer than stored blood, from which it can be recovered; and it may be given without previous tests for compatibility. Serum was found to have similar properties. Finally the problems of storage and ultimately transportation were greatly simplified by the elaboration of techniques for drying plasma and serum, founded on the work of Flosdorf & Mudd (1935) in America and the extension of this by Greaves & Adair (1936) in Britain; when needed, they were reconstituted on the spot by the addition of sterile distilled water or physiological saline. Liquid plasma and serum are unstable and tend to precipitate slowly during storage; dried plasma is stable but involves the transport of two bottles instead of one. Hence attempts have been made to produce a stable concentrated solution, of which the most successful is that of Cohn and his associates in America. This involves the alcohol fractionation of plasma proteins and the use for transfusion of the albumin only, in the form of a 30% solution (various globulin fractions being used for other purposes). Attempts to dispense completely with the human donor have led to trial of other proteins in solution—bovine plasma albumin (as such or after

treatment to remove species specificity), gelatin, isinglass, etc. The consensus of opinion at present favours human plasma proteins, and in Britain difficulties of supply rule out the large-scale preparation of albumin.

All these advances in procedure have been highly developed in Britain, and so well have transfusion services been organised that they are available to the wounded—whether in battle or in civil air raid—during the earliest phases of treatment; a magnificent achievement which not only reduces immediate mortality but also brings the possibility of operative surgery to a high proportion of wounded.

ii. *Restoration of flow through the injured artery*: After wounds of major vessels, the ideal is to restore the flow of blood through its previous channels, or at least to keep up the flow temporarily until an adequate collateral circulation is established. The latter procedure has been attempted by the substitution of various types of cannulae (Tuffier, 1915; Blakemore, Lord & Stefko, 1942) for the normal conduit, and has the theoretical advantage of availability at an early stage of treatment. The former involves the suture of arterial wounds, the anastomosis of severed arteries, and the closure of fistulae between arteries and veins, techniques which demand a much more elaborate operative setting and therefore deferment to a later stage of treatment. In the past, results of both types of procedure have been vitiated by the occurrence of thrombosis within cannulae or at suture lines; but within recent years the discovery of anti-coagulant substances (heparin—Howell, 1916; Charles & Scott, 1933; dicoumarin—Campbell & Link, 1941; Butt, Allen & Bollman, 1941) has provided means by which, under adequate laboratory control, this complication may be prevented or minimised. Many such conditions (traumatic aneurysms, fistulae) are best dealt with after an interval, and vascular centres have been set up, both in the battle areas and in Britain, where they can be dealt with under the most advantageous conditions.

iii. *Surgery of the sympathetic*: The development of the surgery of the sympathetic system has provided a method of modifying the circulation in an extremity. From a surgical point of view, the story begins with Claude Bernard who, in 1852, described the raised cutaneous temperature and increased fullness of subcutaneous vessels in the ear of the rabbit, after section of the ipsilateral cervical sympathetic trunk; then Brown-Séquard showed that stimulation of the trunk was followed by vasoconstriction. In the latter half of the 19th and the beginning of the 20th century the work of Gaskell, Langley and their school solved many problems in the anatomy and physiology of the sympathetic system, and by 1921 the work of Langley, Elliot and Cannon on sympathetic mechanisms, and Dixon, Loewi and Dale on parasympathetic mechanisms, had identified the humoral substances concerned in the mediation of nervous impulses traversing these systems.

In 1913 Leriche utilised as a therapeutic measure the temporary vasodilatation which follows the removal of the adventitial coat of the main artery of an extremity; but it was not until 1924 that Hunter and Royle noted the increased warmth which followed sympathetic ramisection in man. Since that date the operative technique of sympathectomy designed to modify circulation has been modified and revised many times. In Britain fundamental work of this kind has been done by Gask, Telford and Ross, while in the United States Adson and J. C. White have made notable contributions. White has also standardised methods of blocking the paravertebral sympathetic chains by the injection of procaine and alcohol. On the clinical experimental side, the papers of Sir Thomas Lewis and his school have thrown much light on vasomotor conditions, and have supplied not only a wealth of observations but also simple methods of studying such cases at the bedside and in the laboratory. The "war-baby" of this group, immersion foot, has found admirable British expositors in Ungley, Blackwood and Critchley.

It seems clear, from the work of Theis (1933) that, in the experimental animal, division of the appropriate sympathetic nerves will increase the total input of blood into a limb. Both in animals and in man, most of the increased flow traverses the subcutaneous vessels, muscle-tissue profiting less; but experience at vascular centres, both in Britain and abroad, supports the view that when ligation of a main artery in an extremity is inevitable, the risk of massive gangrene can be reduced by a preliminary sympathectomy, which allows a proportion of alternative vascular channels to dilate without the impediment of constrictor tonus imposed by their

extrinsic nerves. It is also possible that, until the casualty reaches suitable operative facilities, the same advantage may accrue, although temporarily, from paravertebral blocking by local anaesthetics of the appropriate sympathetic trunks.

iv. *Reduction of local metabolic rate*: It is a physiological commonplace that the direct application of heat to a part increases its metabolism, and therefore its demand for blood. When the part is ischaemic, a proportion of its impoverished blood supply is diverted by local heating to provide for increased local metabolism, and the total input of blood may ultimately be inadequate to maintain merely the vitality of the tissues, with the result that they die, and more or less extensive portions become gangrenous. Largely as a result of the teaching of Sir Thomas Lewis, the practice of heating locally parts threatened by gangrene has been abandoned; thus the ischaemic limb of the arteriosclerotic or diabetic patient is to-day not deprived of its chances of recovery by the application of hot water bottles or the heat cage. Indeed the modern trend is actively to cool an ischaemic extremity, as tissue metabolism may be reduced by the local application of cold, and at a lower level of tissue metabolism there is a corresponding reduction in the threshold blood supply required to maintain vitality. The therapeutic application of cold in the treatment of threatened gangrene has been studied by Allen (1941 and later), who showed experimentally

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that when an extremity was excluded from the general circulation by a tourniquet, the period over which tissue remained viable was extended by cooling the limb to a temperature of about 5° C. Moreover, this lowered temperature also put an effective brake upon the multiplication and invasiveness of bacteria. These two effects of chilling have an obvious application in war wounds, especially in cases in which arterial injuries leading to a reduction in the circulation of a limb may be disastrous as a result of the rapid spread of anaerobic and aerobic infections; and the principle has been put to material use in the present conflict.

v. *Prevention and management of lesions due to cold*: Nutritional lesions following prolonged exposure to cold (immersion foot) or severe cold (frostbite) may, in many instances, be prevented by suitable precautions on the part of those undergoing such risks, and much successful work has been done in improving conditions at sea, on land and in aircraft. When exposure is inevitable, every precaution has been taken, by the education of personnel,* to minimise its consequences. Moreover, as a result of experimental work and the collection and scrutiny of clinical records, the treatment of resulting lesions has been established on the broad biological principles indicated above; and there has emerged a balanced conservatism which has been saving of both life and limb.

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* [see BMB 403 & 404]

290

INJURY FROM EXPOSURE TO LOW TEMPERATURE: PATHOLOGY

W. BLACKWOOD, M.B., CH.B., F.R.C.S.ED.

When parts of the body are exposed to temperatures increasingly below that of their customary environment, they become "chilled." A tissue is said to be "chilled" when it has been damaged by exposure to a low temperature of a degree insufficient to cause frostbite. At first, normal physiological mechanisms are able to compensate for the cooling, but as the environmental temperature falls, and especially if loss of heat from the exposed part is accelerated by immersion in cold water or contact with cold metal, a level is reached when tissue damage occurs from which recovery is possible. Still lower levels of cold cause irrecoverable tissue changes. These temperature levels probably vary for the individual tissues of the part. Lewis (1942) has shown that recoverable damage may involve skin and subcutaneous tissues at a temperature from 18° to 15° C., and that irrecoverable damage by freezing occurs between - 5° C. and - 10° C. The fact that they do not become frozen at their true freezing point (about - 2° C.) is due to the ability of the skin to supercool.

The sequel to tissue damage is an inflammatory reaction or necrosis. The onset and rate of the inflammatory process depends upon the blood flow through the tissue; it proceeds slowly while the tissue is still chilled, and is accelerated by warming. It is thought that inflammatory oedema causes circulatory obstruction, and so additional tissue damage. Repair follows in parts less seriously damaged; dead tissues form sloughs.

Various degrees of chilling and differing environmental features give rise to different clinical manifestations with distinct clinical and histological features.

Immersion Foot

This is a condition in which the limbs are exposed for periods of about 22 hours or longer to moist conditions or to immersion in sea water, at temperatures from 10° C. to - 1.9° C. (Ungley & Blackwood, 1942). Damage of varying degree is caused to all the tissues of the limb. The damage to the skin is the most obvious, and results in blisters or gangrene. The damage to nerves, muscles and blood vessels is less obvious, but it is the cause of the prolonged disability

from which the patients may suffer. The nerves show extensive demyelination of a degree and to a level depending upon the severity and extent of the exposure (Blackwood, 1944). All fibres are affected, especially the smaller myelinated and unmyelinated fibres. After rescue of the patient the nerves regenerate slowly, but perhaps incompletely. Incomplete regeneration is often associated with pain. This may be due to fibrosis of the superficial nerves (White, 1944), or to the transmission by incompletely regenerated nerves of impulses which cannot be normally synthesized and which are interpreted as pain.

In experimental animals the muscles show partial hyaline necrosis (Blackwood & Russell, 1943), followed by partial regeneration, and also by secondary degenerative changes due to denervation. Fibrosis of muscle is not a noticeable feature. The blood-vessels, which have been in spasm during exposure, dilate when the patient is warmed. In the experimental animal, they may show intimal swelling and damage to the media (Smith, Ritchie & Dawson, 1915) in the acute stage, but in man little evidence of this is to be seen in the later stages. Intravascular thrombosis is found only in veins and only near regions of necrosis or chronic infection. There is often a disturbance of the neuro-vascular mechanism, resulting in a state of cold-sensitivity, the pathological basis of which has not been demonstrated. Bones often show initial osteoporosis, followed by recalcification.

Frostbite

This condition may occur when portions of the body are exposed to temperatures below about - 5° C. Superficial tissues are rapidly chilled and there is crystallization of tissue fluids, rupture of cell walls, and death of tissue from the direct effect of the cold. When the exposure is of short duration, only the skin and superficial tissues are killed; the deeper tissues remain intact because there has not been time for their cells to be much chilled. After longer exposures more tissue is irretrievably damaged. Stasis of blood occurs in the vessels, but thrombosis is not a feature of the exposure period (Greene, 1943).

Later an inflammatory response appears, with blistering,

PHOTOGRAPHS ILLUSTRATING THE PATHOLOGY OF IMMERSION FOOT

A. Human material



FIG. I—Dorsum of foot 50 days after exposure for 8 days on a Scottish hillside in cold and wet weather. On examination 6 days after the exposure, the hyperæmic stage of immersion foot was present. Both feet were similarly affected, with commencing gangrene in the toes. The great toe shown in this picture was subsequently amputated.



FIG. II—Lower extremities seen 4 months after a 10-day exposure in an open boat in the North Atlantic in November. The gangrenous feet had already been amputated when this photograph was taken. The wounds did not heal and there was severe pain. The legs were amputated below the knee.

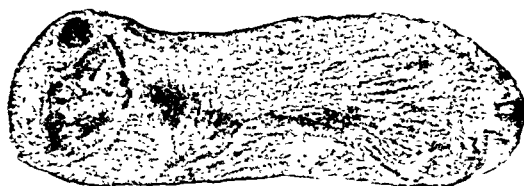


FIG. III—Foot amputated 26 months after exposure for 10 days in an open boat. Before amputation the toes were missing and the skin was severely ulcerated, especially in the region of the os calcis, which was exposed. Same case as Figs. VIII and IX.



FIG. IV—Longitudinal section ($\times 90$; haematoxylin and eosin) of extensor digitorum brevis muscle showing extensive muscular degeneration (Zenker's hyaline degeneration). Specimen from a man, exposed in an open boat for 34 hours in cold wet weather, who died half an hour before rescue. As judged from the condition of two survivors, he would have shown a moderate grade of immersion foot.



FIG. V—Longitudinal section ($\times 225$; myelin stain) of interdigital nerve of toe, removed 10 weeks after exposure in an open boat for 21 days. From a moderately severe case of immersion foot without gangrene. There has been severe degeneration, for only one normal myelin sheath (A) is seen. Globules of degenerate myelin are seen (B) and proliferated Schwann cells (C). There were sensory and motor changes in the lower limbs.

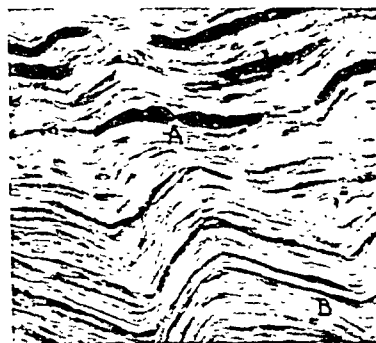


FIG. VI—Longitudinal section ($\times 225$; myelin stain) of tibial nerve in lower third of leg, 10 months after exposure for 5 days in an open boat in severe weather. The patient suffered from a severe grade of immersion foot, and continued pain necessitated amputation of both legs. The section shows thick fibres (A) which escaped destruction and then regenerating fibres (B).

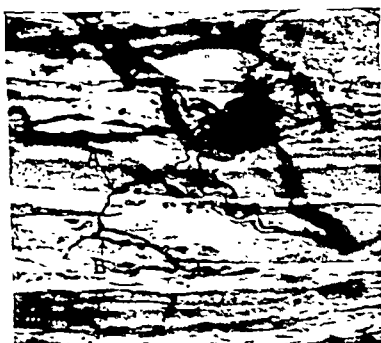


FIG. VII—Longitudinal section ($\times 265$; axis cylinder stain) of thenar muscle of right hand 12 months after exposure in the sea for $\frac{1}{2}$ an hour and in an open boat for 22 $\frac{1}{2}$ hours in severe weather. Severe case without gangrene. The nerves are now returning to the muscle fibres which escaped destruction. A regenerating axon has grown out from its old neurilemma (A) and formed a nerve network (B) between the muscle fibres.

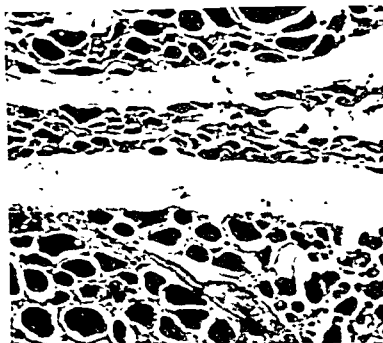


FIG. VIII—Transverse section ($\times 90$; haematoxylin and eosin) of flexor hallucis longus of the foot shown in Fig. III. Muscle damage is unevenly distributed, as shown by the variation in calibre of muscle fibres.



FIG. IX—Transverse section ($\times 10$; myelin stain) of tibial nerve 6 cm. above extremity of lateral malleolus. Same case as Figs. III and VIII. The relative pallor of the nerve bundles indicates marked demyelination, persisting after 26 months.

[Figs. I-IX were first published in the paper reviewed in BMB 401 and are reproduced by permission of the author and of the editor of the British Journal of Surgery.]

PHOTOGRAPHS ILLUSTRATING THE PATHOLOGY OF IMMERSION FOOT

B. Animal experiments

The illustrations are all of tissues from rats' tails which had been immersed for 96 hours in artificial sea-water at 4°-5° C.



FIG. X—Longitudinal section ($\times 350$: myelin stain) from rat killed immediately after exposure. The nerve on the left shows slight irregularity of contour. The muscle fibre on the right shows hyaline necrosis.



FIG. XI—Longitudinal section ($\times 350$: myelin stain) taken from rat killed 3 days after exposure. The nerve fibres are degenerating, and many muscle fibres are degenerate.



FIG. XII. Longitudinal section ($\times 350$: haematoxylin and eosin) taken from rat killed 3 days after exposure. Marked cellular reaction in the damaged muscle fibres.



FIG. XIII—Longitudinal section ($\times 350$: myelin stain) from rat killed 30 days after exposure. Increased cellularity of a muscle nerve, only one myelinated fibre remaining in the leash, which runs obliquely across the top of the picture. Shrunken muscle fibres are seen below, often with only a narrow strand of surviving myoplasm.



FIG. XIV—Longitudinal section ($\times 350$: myelin stain) from rat killed 30 days after exposure. Main nerve of tail, showing numerous degenerate fibres.



FIG. XV—Transverse section ($\times 85$: haematoxylin and eosin) taken from rat killed 60 days after exposure. Changes are still present in muscle and nerve tissue.

[Figs. X-XV were first published in the paper reviewed in BMB 398 and are reproduced by permission of the author and of the editor of the Edinburgh Medical Journal.]

sloughing of dead skin or deeper tissues, and subsequent re-epithelialisation. Thrombi are now found in the arteries and veins of the skin and subcutaneous tissues, both in the necrotic regions and in those adjacent (Lewis, 1941). Obliterative endarteritis is reported to occur proximal to the necrotic area (Ducuing, d'Harcourt, Folch & Bofill, 1940, quoted by Bigelow, 1942). In frostbite, as in immersion foot, a state of vasoneuropathy and cold-sensitivity may develop after exposure. Detailed observations on the peripheral nerves do not seem to have been described. The bones show osteoporosis. Tissues affected by frostbite, like those damaged in immersion foot, are very liable to chronic pyogenic infection.

The pathological changes in high altitude frostbite have recently been reported by Davis, Scarff, Rogers & Dickinson

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392

INJURY FROM EXPOSURE TO LOW TEMPERATURE: CLINICAL FEATURES, PREVENTION, TREATMENT

R. L. RICHARDS, M.B., CH.B.

The clinical features observed in an extremity after exposure to cold depend upon the duration and severity of the exposure. Brief exposure to severe cold results in freezing of tissues (frostbite); because they possess the property of super-cooling, the temperature may fall to a level below tissue freezing point before frostbite occurs. A short, stinging pain may be felt; the affected area becomes hard, white and brittle, and remains so until thawing begins, when a red flush develops around it and gradually invades it. Blisters may form, and there is extravasation of serum and blood in the part, which leads to swelling and possibly to occlusion of its blood-vessels so that distal portions of an extremity, already endangered by freezing, become gangrenous. If infection is avoided, the end-result of severe frostbite is dry gangrene similar to that observed in severe forms of any type of peripheral vascular disease. Tissues immediately adjacent to the frostbitten area remain normal.

A more prolonged exposure to degrees of cold insufficient to cause freezing causes "chilling" of the tissues. This is the pathological basis of immersion foot, trench foot and allied conditions. During the period of exposure the distal parts of the affected extremities become numb, are usually white or yellowish in colour, and after a time begin to swell. When the extremities are removed from the cold environment, they pass through three consecutive phases which have been described as *prehyperæmic*, *hyperæmic* and *posthyperæmic* (Ungley & Blackwood, 1942). The *prehyperæmic* stage is a direct continuation of the clinical picture during exposure; the feet and legs are cold, swollen, pulseless, feel numb, exhibit objective loss of sensation of glove or stocking type, and motor activity in digits is impaired. Within hours, or in severe cases 1 to 2 days, a rapid change takes place to the *hyperæmic* stage; they become hot, flushed or pale, the pulses are full and bounding, and the patient complains of severe pain. The pain is usually of two types: (1) a severe burning aching pain felt in the hand or foot, and (2) short, shooting, lancinating pains which radiate into the digits; both types of pain are related to and aggravated by warmth, and are relieved by cold. In this *hyperæmic* stage there is every evidence of an exceedingly active circulation; if the extremity is dependent it becomes a deep reddish-purple, and on elevation it blanches almost instantaneously. Swelling increases, and blisters may form over pressure points and at the sites of unnoticed injuries sustained during exposure. Portions of the extremities destined to become gangrenous fail to warm, remain at first whitish or purple in colour, and finally become black and shrivelled. The area of objective sensory loss recedes towards the periphery; but remains of glove or slipper type, and there is anhidrosis of the soles or palms. The initial intense *hyperæmia* lasts for 7 to 10 days. Mild

(1943). In the hands the initial immediate response is constriction of the terminal portions of the superficial arterioles. Damage to the endothelium of the terminal cutaneous capillary loops results, after exposure, in transudation of fluid, or there may be thrombosis at the arteriolo-capillary junction. These changes produce large blisters, the line of separation being deep to the basal germinal layer of the epidermis; thus subsequent reformation of the epidermis is slow and derived from remnants of germinal epithelium persisting in the ducts of glands. When the exposure is sufficiently severe for the deeper arterioles to be injured, dry gangrene ensues. There is immediate loss of nerve function; and concentric intimal fibrosis of the digital arteries proximal to severe cutaneous lesions, and later prolonged vasoneuropathy have been recorded as sequels.

cases may pass from this to normality, but the majority exhibit a less intense hyperæmia lasting for 4 to 6 weeks. After this period the previously warm extremities show signs of vasomotor instability, and on occasion may be cool or cold. As time goes on the extremities tend to remain cold, and enter the *posthyperæmic* stage, in which they exhibit undue sensitivity to cold, which may take the form of attacks of the Raynaud phenomenon in the digits. Return of sensation is by nerve regeneration, and this is accompanied by the sensory phenomena which are associated with recovery from any nerve injury. When swelling subsides, wasting of the intrinsic muscles of the feet or hands becomes apparent, giving rise in the hand to an appearance like that of progressive muscular atrophy, and in the foot to clawing of the toes and a flat-footed springless gait. Another feature of this phase is hyperhidrosis, most marked in response to emotional or noxious stimuli. In the most severe cases gangrene occurs, with loss of digits and more rarely loss of hand or foot. Late sequels include persistence of a cold-sensitive state in the extremities, recurrence of pain when walking is resumed, deformities of the feet and absence of healing in the ulcers left under blisters or after removal of gangrenous tissue. Symptoms may persist for several years after exposure, and those who have been exposed to the effects of cold are more susceptible if re-exposure occurs.

High altitude frostbite recently described by Davis, Scarff, Rogers & Dickinson (1943) appears to occupy an intermediate position between acute frostbite and the syndrome resulting from chilling. A "wet type" associated with much œdema and blister formation, and a "dry type" corresponding to the classical picture of frostbite are described.

Prevention of frostbite is by adequate protection of the extremities, and this is usually possible under the conditions in which frostbite is likely to occur. Prevention of immersion foot is more difficult. The steps that may be taken have been fully outlined by the *Medical Research Council* (1943). Maintenance of the warmth of the body and avoidance of prolonged periods of immobility, of constriction of the limbs, and of injury to numb and swollen extremities are all of importance. Rubbing the feet with grease probably does more harm than good, but the wearing of stockings impregnated with vaseline is now advocated.

In the treatment of the established conditions, the aim is to avoid too rapid warming of the affected extremities. These should be elevated and exposed to the air in a cool environment; if a fan is available, it may be used to cool them; in hospital the use of cooling cabinets or icebags may be tried, but cooling should not be too intense, the aim being to maintain the temperature of the extremity in the neighbourhood

of 20° C. Once hyperæmia has developed, cooling is of definite value for the relief of pain. The direct application of heat has no place in the treatment of the chilled extremity. Indirect measures to increase the circulation such as reflex vasodilatation, vasodilator drugs, sympathetic block by local anæsthesia, and sympathectomy are of doubtful value; there is the danger that they may increase intravascular pressure and thus cause greater damage by increasing exudation. The extremities should be kept surgically clean;

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¹ [see BMB 403]

blisters are snipped with sterile precautions and raw areas are dressed with sulphanilamide and paraffined gauze. A prophylactic dose of anti-tetanic serum should be given. An attitude of surgical conservatism is called for; in the early stages the appearance of an extremity in which eventually only the tips of the digits will be lost may be most alarming. Amputations of the trimming variety are usually all that are required. In the late stages preganglionic sympathectomy may be of value in dealing with the cold-sensitive state.

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393

TREATMENT OF ARTERIAL INJURIES

B. C. MAYBURY, M.B., B.S., F.R.C.S.

The treatment of arterial injuries in warfare is best considered under two headings: (a) the early treatment shortly after the infliction of the wound, and (b) the treatment of traumatic false aneurysm and the two varieties of arteriovenous fistula which may result from certain types of injury.

A. Early Treatment

Immediate control of hæmorrhage: In the forward battle area where only first aid is available, control is effected, in order of preference, by local pressure, application of forceps left *in situ*, ligature and, as a last resort, the application of a tourniquet; the last must be regarded as a confession of failure.

Treatment at centres where adequate facilities exist and where the patient can be retained: The treatment of the injury depends on the nature of the damage to the artery which may be: (i) complete division; (ii) partial division; (iii) contusion: (a) with thrombosis, (b) without thrombosis; iv) arterial spasm.

Complete Division

The ideal of an axial anastomosis is rarely admissible in high-velocity wounds, as the damage to the severed ends by the "lateral concussive effect" of the projectile and the necessity for excising the damaged ends, results in a gap which makes impossible an anastomosis without tension; here is also the risk of infection which may lead to necrosis of the suture-line. This method may, however, be employed in stab wounds, e.g. by bayonet, in which there is no necessity to trim the severed ends and there is little or no risk of infection. To prevent thrombosis, the commonest cause of failure, heparin should be given intravenously, if other wounds in the same patient do not contra-indicate its use.

The use of an artificial cannula, the Tuffier's tube, or fine variety of Whipple's cannula, which is inserted in the gap and over which the severed ends of the artery are tied, provides a free flow of blood through the main artery for 3-4 days if heparin is given to prevent thrombosis. The cannula must be removed at the end of this period and both ends of the artery must be ligated. The time thus gained enables some degree of collateral circulation to be established and is valuable in reducing the risk of a rapidly spreading infection, anaerobic or aerobic, or ischæmic necrosis or both. The cannula should be of a slightly smaller diameter than that of the lumen of the artery to provide a stimulus for the developing collateral circulation.

A second variety of Whipple's cannula consists of two small metal tubes which unite a free vein-graft to the severed ends of the artery. The whole is intended to remain permanently *in situ*. Heparin should be given. This method should not be used in heavily contaminated wounds.

If the above methods are not practicable, both ends of the artery must be ligated, but often the limb has to be amputated within a few hours for a fulminating anaerobic infection or later for ischæmic gangrene. Among the limb arteries the popliteal, and the upper part of the posterior tibial, have the worst prognosis in this respect.

A primary amputation is the best procedure when there has been much muscular damage at the level of arterial severance, potential collateral vessels having been thereby destroyed.

ii. Partial Division

(a) *With small entry and/or exit wounds in the overlying soft tissues:* The imbrication of the various layers of muscle, fascia and skin across the track of the projectile prevents serious external hæmorrhage and the result is an arterial hæmatoma or early stage of false aneurysm, or if the vein has been wounded as well, an arteriovenous fistula. The diagnosis of this type of injury depends mainly on the presence of a short systolic murmur which is usually evident a few hours after the injury, although its appearance may occasionally be delayed. It is essential to recognise that the volume of blood flowing through the main artery is usually sufficient to cause no appreciable change clinically in the distal pulse and, nearly always, to ensure that there is no serious ischæmia of the limb. Although operations for these false aneurysms are eventually required, they are not often necessary in the first week, during which there is an adequate volume of blood flowing through the main artery and a progressive increase in the collateral circulation. By early operative interference the surgeon is therefore doing harm. These cases should be carefully watched, the limb should be immobilised and operation should be undertaken only if suppuration occurs, or if the pressure of the enlarging sac begins to interfere with the collateral circulation or with the flow through the main artery distal to its wound. Sometimes an incision through the deep fascia in the soft tissues away from the wound will relieve the pressure of an increasing hæmatoma and the distal pulse will return at once, though not always permanently.

(b) *With large entry and/or exit wounds in the overlying soft tissues:* As there is no soft-tissue barrier to the escape of blood externally, such cases do not often reach an operating centre without the previous application of forceps or ligature. Because he fails to realize that the presence of a distal pulse is not necessarily evidence that the artery is intact, and because he fails to auscultate the wound, a surgeon may proceed to excise a relatively small wound in the soft tissues, and may be confronted with a lateral wound in the main artery.

Suture of the arterial wound, as previously stated, is not often advisable; moreover, a longitudinal suture may cause so much narrowing of the lumen as almost or completely to obstruct the blood-flow. It may, however, be tried in stab wounds, especially if the artery is large and its wound small. Heparin should be given.

The method most likely to prove successful is to imitate Nature by making a barrier of soft tissues by suturing one or two layers of fascia or muscle over the artery and its wound, with the deliberate object of allowing a false aneurysm to develop and thereby maintaining a blood-flow through the main artery. Heparin should not be given.

The use of an artificial cannula, though technically easy, is not so effective, as the artery must be ligated not later than the fourth day. The artificial barrier method ensures the main arterial blood flow, usually for at least a week and often much longer.

iii. Contusion

(a) *With thrombosis:* Axial anastomosis is never possible owing to the length of the artery that must be excised.

An incision should be made through the normal vessel proximal to the clot, which is extracted, and the arterial wound is then sutured. A layer of muscle or fascia is sutured over the vessel to prevent external hæmorrhage if part of the arterial wall should subsequently necrose. Heparin should be given.

If the above procedure is not possible, an artificial tube should be used.

(b) *Without thrombosis*: This injury is not diagnosable clinically, but is discovered during the primary excision of the wound in the soft tissues. As the contused portion may slough and separate from about the fifth day, it is desirable to provide a barrier of muscle or fascia to ensure the formation of a false aneurysm and hence maintain the main arterial blood-flow, and also to prevent a serious external secondary hæmorrhage.

iv. Arterial Spasm *

Arterial spasm is not commonly produced by gun-shot wounds and is impossible to diagnose clinically from other arterial injuries which interrupt the main blood-flow.

If arterial spasm is seen during the course of the operation, the vessel should be gently washed with saline. Periarterial sympathectomy should not be done. If there is much damage to the prospective collateral vessels, the artery may be forcibly distended by the proximal injection of the vessel with saline. The condition often disappears spontaneously within 24 hours.

Treatment of the Ischæmic Limb

When the main arterial supply to a limb has been interrupted by ligature or injury, attempts should be made to reduce the demands on the limited blood available and if possible to increase the quantity and quality of blood.

The limb should be kept cool and at rest by wrapping in wool on a well padded splint and suspending it from a cradle from which ice-bags are also suspended. No pressure, either by bandage or splint, should be allowed to occur at the level of the collateral vessels. The limb should be elevated to prevent œdema, which would compress the capillaries.

Large transfusions of blood (in preference to plasma) should be given and oxygen should be administered by the B.L.B. mask. Warming the rest of the body by radiant heat or hot water bottles and immersing the unaffected limbs in hot water will increase the vascular dilatation of the affected limb.

The value of sympathetic block is still under discussion, but there is much clinical and experimental evidence, especially in the case of the lower limb, to show that sympathectomy increases the rate and volume of the collateral circulation. Although it is undesirable that a patient with a seriously wounded limb should be subjected to the major operation of lumbar sympathectomy, the same but temporary effect can be obtained by a local lumbar injection of procaine, or better, procaine in oil.

Measures should be taken to combat infection, which is a common and serious risk in an ischæmic limb when the wound is contaminated.

It is generally agreed that when the main artery has been tied, the main vein should be tied as well; this procedure is, however, not universally accepted.

At a later stage, when natural warmth has returned to the limb and capillary return is normal, active muscular movements will help still further the collateral circulation.

B. Late Treatment : Traumatic False Aneurysm and Arteriovenous Fistula

The partial division of an artery, if treated expectantly, or by a musculo-fascial barrier, will inevitably lead to a traumatic false aneurysm; or if the vein has been wounded as well, either to an aneurysmal varix or varicose aneurysm. Almost all false aneurysms are formed in this way, though a few may result from the rupture of a contused portion of the wall of the artery, the lumen of which has remained patent throughout.

i. Traumatic False Aneurysm:

Operation is always required sooner or later, because the slowly but progressively enlarging sac will press on adjacent nerves, on the collateral circulation or on the distal portion of the main artery. The longer operation can be delayed, the greater will be the collateral circulation, the less the risk of ischæmia resulting from the usually necessary ligature, the easier its technical performance, and the less the risk of

lighting up a dormant infection. On the other hand, the time of operation may have to be advanced owing to the appearance of one of the complications mentioned below. The time that should elapse between the date of the wound and the operation depends on many factors and varies greatly, but in general should be 2-4 months, and it should be longer in the case of the lower than the upper extremity. During the period of waiting, the muscles surrounding the sac should be kept at rest, but those of the distal portion of the limb should be given active movements to assist in the further development of the collateral circulation.

Although arterial suture may be attempted, especially of a small wound of a large artery, the operation is more difficult and not so certain in its results as the simpler one of ligature. Moreover, the longer operation is postponed, the less is the necessity for retaining the patency of the main vessel. In performing suture, arterial wall should be sutured to arterial wall, and no part of the false sac should be used to cover the opening. A double ligature is applied immediately proximal and distal to the arterial opening and any branch opening into the sac is also ligatured. Remote proximal ligature should not be done, as the aneurysm recurs and the second operation is much more difficult owing to the direct or indirect entry into the sac of several unknown and unmapped arteries.

For the temporary control of hæmorrhage, the use of a tourniquet, preferably pneumatic, is best. If this is impossible, the artery must be exposed above and below the sac, and either temporary clamps must be applied or tapes, tied gently but firmly with a single hitch over short lengths of rubber tube, must be used as ligatures. When the operation is completed the tapes are easily cut with a knife, the edge of which is directed towards the rubber. While it is important to obtain an adequate exposure of the artery and sac, it is also important to divide as few branches not connected with the sac and as little muscular tissue (which contains many arteries) as possible; these vessels may be vital components of the collateral circulation. The sac is next freely incised and, while an assistant places a finger over the opening of any branch entering it, the surgeon working from inside the sac separates the artery from it for a short distance above and below the arterial opening. The artery is then ligatured immediately above and below the opening and divided between the ligatures. Any branches opening into the sac are similarly ligatured. Not only is there no necessity to remove the sac, but attempts to do so are difficult and may damage nerves incorporated in its wall and important components of the collateral circulation.

Occasionally, when immediate proximal ligature is impossible, a distal ligature may succeed if no other branches enter the sac or enter the vessel between the ligature and the sac.

Complications of traumatic false aneurysm: The treatment of pressure on the collateral vessels by an arterial hæmatoma in the early stages has already been mentioned under A (ii) above.

At a later stage internal hæmorrhage, as indicated by a sudden increase in size of the swelling, is caused by a leak at the junction of the attachment of the sac to the edges of the arterial wound. It is usually due to inadequate immobilization but may be due to sepsis. If due to the former it is treated expectantly provided the distal pulse is present but, if absent, by a separate fascial incision. If this fails the artery must be ligated. Suppuration sometimes occurs, usually during the second week, and its situation is at the junction of the clot with the surrounding tissues. It is treated by incision and ligation of the artery.

In the later stages, compression of adjacent structures, especially the vessels of the collateral circulation, may necessitate the advancement of the time of operation. Involvement of adjacent nerves is not of necessity an indication for interference; when operation is eventually performed the nerve recovery is often very rapid. Œdema due to pressure on veins and lymphatics is treated by keeping the limb elevated.

ii. Aneurysmal Varix and Varicose Aneurysm

Operation for varicose aneurysm is always eventually required because of the progressively enlarging sac. However, as the rate of growth is slower than that of a traumatic false aneurysm, owing to the safety-valve effect of the opening into the vein, operation can usually be postponed for a longer period.

* [see also BMB 394]

Operation for aneurysmal varix may never be required, as the fistula tends to contract and, if small, may close spontaneously. The chief danger is the strain on the heart produced by the persistent tachycardia; rarely this may cause death within a few days, but usually the effects are not noticed for several months or even years. In general, therefore, all persistent aneurysmal varices should be operated on, but only after the lapse of some months or even longer if the tachycardia is not severe. The audibility to the patient of the bruit caused by arteriovenous fistulæ in the head and neck may affect his mental state and may necessitate the earlier performance of the operation. As other complications of arteriovenous aneurysm are uncommon, and of aneurysmal varix rare, early operation is not often necessary in the former and rarely in the latter.

During the early stages, the affected part must be immobilized and throughout there must be a reasonable amount of rest of the body to reduce the strain on the heart.

The remarks on arterial suture for the treatment of traumatic false aneurysm have a similar application to arteriovenous fistulæ. If used for the cure of an aneurysmal varix, the best approach is through the vein, the latter being subsequently ligatured.

The classical operation is the "quadruple ligature," i.e. immediate proximal and distal ligature of both artery and vein; in varicose aneurysm the sac must be opened and any branches opening into it must also be ligated. Proximal ligature of the artery alone must never be done; the limb would bleed to death through the fistula into the vein. Distal ligation of the artery alone would compel more blood than ever to enter the vein, and is therefore not permissible. In aneurysmal varix, the dense adhesions which bind the artery and vein together for a considerable distance above and below the fistula may make difficult the determination of the exact site of the fistula, which can be ascertained by noting the position where the murmur is loudest and of the highest pitch.

TRAUMATIC ARTERIAL SPASM

SOL. M. COHEN, F.R.C.S.

Two main types of traumatic arterial spasm may be distinguished (i) the purely local response to direct trauma; (ii) a more widespread spasm, with minimal or no direct vascular trauma, but associated with other severe tissue damage, often local, which may give rise to shock.

i. Local Spasm following Direct Trauma

That the arterial wall contracts in response to an injury is well known, but the exact mechanism of this response is open to argument. It has been maintained (Leriche, 1939) that the local periarterial sympathetic plexus provides an intrinsic mechanism for such spasm; that the bruised vessel initiates a purely local "automatic" reflex, or one via the sympathetic ganglia. It has also been maintained (Leriche, 1937) that a damaged vessel "reflexly" maintains a state of spasm of the collateral vessels, and excision of a segment (arteriectomy) has been recommended as a necessary measure to abolish this collateral spasm. Nevertheless there appears to be reasonable doubt as to the existence of any such local reflex mechanisms.

This question is of more than academic importance, for the nature of treatment will depend on it. Anatomists (Woollard, 1926; Le Gros Clark, 1939) deny that any local arterial ganglion cells exist: no afferent sympathetic arc has ever been found, and the pathways for such reflexes are speculative. Clinical evidence is strongly against such a local mechanism. No reflex can explain why spasm should last sometimes minutes, sometimes hours, sometimes days. Procaine abolishes all nerve conduction; it should always and immediately abolish such "reflex" spasm if infiltrated around the vessel wall, but it does not. Bruising of vessels is common in the course of operations or injuries—yet persistent spasm is rare; the sutured vessel, after embolectomy or repair, will pulsate fully, despite the damage caused by tension of sutures.

For these reasons it has been urged (Cohen, 1941, 1944) that the key to the understanding of the peculiar and differing responses of vascular spasm lies in the appreciation of the natural contractile properties of the smooth muscle of the arterial wall. Smooth muscle responds only to a particular type of stimulus; this may be demonstrated in the bowel, which does not respond to cutting or pinching, but requires a definite type of stimulus—distension—to make it contract. Similarly with the vessel: a particular stimulus—a stretch-stimulus, or alteration in length of the muscle fibres—is required to initiate spasm. The local arterial bruise may thus be regarded not as an irritable focus, but as visible evidence that the vessel has sustained a severe blow.

In traumatic arterial spasm, the fibres of smooth muscle may decrease to $\frac{1}{2}$ of their resting length, and the contracted vessel may appear as a mere thread. Smooth muscle needs little oxygen to maintain its new length, and the vessel can survive and maintain a state of spasm even whilst the tissues around are dead or dying (C. W. Clark, 1943).

Influence of the sympathetic: It may well be asked: what is the function of the interlacing periarterial sympathetic fibres? It would appear that the sympathetic system of the limb is best viewed as an effector mechanism—one of a

number—for controlling the circulation. The sympathetic supply to the deeper vessels, compared with that to the skin and superficial structures, is relatively poor. The local vascular reflexes are usually concerned with the skin, but in states of emergency, such as shock or asphyxia, major vessel contraction may come into action.

The sympathetic system has been regarded as exercising a deleterious influence on the return of the collateral circulation, and the cold skin of the recovering circulation in the limb has been viewed as Nature's mistake. Of the two measures which have been advocated to release this "pathological" spasm of the collaterals—(a) arteriectomy—to remove an irritable local focus maintaining reflex spasm, (b) procaine block of the sympathetic ganglion—neither results in any sudden return of the circulation. The recovering circulation, as judged by the skin, still appears to creep slowly down the limb. It has been demonstrated that the cold pale skin may be associated with dilatation of the deep vessels supplying the muscles, and it is becoming increasingly recognised that the muscle circulation cannot be assessed from observation of the skin circulation alone (Friedlander, Silbert & Bierman, 1940; Grant & Pearson, 1938). The prime need of the recovering limb is for the early return of the circulation to the muscles; skin can survive long periods of ischæmia. Sympathectomy will not increase the blood supply to the muscles. The cold contracted skin of the ischæmic limb may be regarded as serving a useful purpose by preventing the accumulation of the limited blood supply in the skin vessels at the expense of the muscles.

Types of Traumatic Arterial Spasm

Several varieties of local spasm following the local vessel injury need separate discussion.

(a) *Spontaneous suppression of hæmorrhage:* Nature's method of sealing the divided vessel is indeed ingenious; the elasticity of the vessel, which speeds the blood flow, also initiates the impulse that seals the flow when the vessel is severed. The elastic tissue in a vessel is in a state of longitudinal stretch; to divide it is to alter suddenly the length of the muscle fibres and to initiate the muscle contraction. Only the muscle fibres adjacent to the point of division are thus affected, and this accounts for the very localised segment of vessel involved in such spasm. Where the recoil of the divided vessel is prevented, contraction is defective. Thus the partially divided vessel continues to bleed; a strip of adventitia or a shred of intact vessel wall will suffice to maintain the muscle length and thus prevent spasm. It is perhaps not sufficiently realised that forcible traction on a vessel, as in embolectomy or in dissection of an aneurysm, may induce prolonged and extensive spasm, especially in the distal vessel segment. This fact has an important practical application, for it emphasises the need for gentleness, and the avoidance of strong pull by artery forceps to deliver the vessel for ligature.

(b) *Arterial spasm following gunshot wound:* After a "near miss" by gunshot or bomb splinter, the vessel may be found in a state of spasm. This is often referred to as *stupeur artérielle* or sometimes as "Kroh's arterial spasm,"

following the description by French and German observers of cases in the 1914-18 war. Usually, it has been an accidental finding in the course of vessel exposure during wound excision; absence of pulse may have suggested it. Only a short segment of vessel may be involved. The spasm is rarely maximal, the lumen being merely narrowed and the distal limb is rarely seriously endangered. There is no evidence in these cases that the collateral circulation is also held in "reflex" spasm. It would appear reasonable to regard this form of spasm as consequent upon the sudden stretching of the vessel by lateral displacement due to the exploding force of the missile. Almost invariably, after inspection of the vessel and removal of adjacent blood clot without further intervention, such spasm disappears within 24 hours—with a satisfactory subsequent result.

(c) *Arterial spasm following fracture*: The importance of arterial spasm as a cause of gangrene or Volkmann's contracture has become increasingly recognised. Minor degrees of spasm are often found to follow fracture manipulations; the pulse disappears, as a rule only for a short period of 20-60 minutes, and there are no indications of nutritional or functional disturbance in the limb. The spasm may, however, last many hours and continue until the death of the limb. That the vessel is in spasm can be decided only by surgical exploration. It is important to remember that spasm is not the commonest cause of suppression of the pulse; often the vessel is divided, sometimes it is thrombosed, and at other times it is stretched over a bone spike, or is caught between the bone ends. It may even be compressed by an increasing hæmatoma.

It is tempting to wait and observe, for we know that such "spasm" often disappears spontaneously; but it cannot be assumed that this will happen, and where there is any doubt about the pulse, it is important to expose the vessel early. If the limb, and especially the muscles, are to be saved, operation must be done preferably within 6 hours of the injury. If the vessel is found to be in spasm, any surrounding blood clot should be gently removed and hot saline applied. Peri-arterial sympathetic stripping is inadvisable, and procaine injection locally or into the ganglia fails to release the spasm.

The degree of spasm varies; if it be mild, the vessel merely narrows and there are no distal ischæmic manifestations. In such cases, the vessel is best left alone, for the spasm will often disappear within a few hours. Plaster casts are contraindicated in such cases, as they may compress the collateral vessels over the bony points. Where the vessel is in very tight spasm—like a string—more desperate measures should be tried. Experience shows that this type of spasm does not relax spontaneously. Forcible stretching of the vessel lumen, by injection of saline under pressure through a No. 17 needle, is worthy of trial. It may be necessary to compress the vessel proximal to the needle point so as to raise sufficient pressure. Reasons for disbelief in the value of arteriotomy have already been mentioned above, and to do an arteriotomy where there is extensive collateral damage is to make certain of disaster.

A particularly obstinate type of vascular spasm sometimes follows fracture or injuries in the region of the popliteal fossa, particularly fractures of the condyles of the tibia, often with no displacement. Such spasm has also followed the use of the Böhler frame or other counter-pressure on the back of the lower end of the thigh. On exploration, some blood-staining of the adjacent areolar tissues may be seen, but there is no visible damage to the vessel. Often the patient has other injuries and has at some time been severely shocked. This type of spasm is distinct from the myogenic variety that we have been considering, and is probably best regarded as a shock response with local vascular emphasis. Its treatment

will be considered in the discussion of the probably allied conditions, crushing injury and tourniquet spasm.

ii. Local Spasm without Direct Vascular Trauma

Under this heading may be considered the type of arterial spasm that follows the "crushing injury" or the tight tourniquet. In the cases of "crushing injury" that followed compression of limbs by fallen masonry (in some air-raid casualties) Bywaters, Belsey, McMichael, Dunn *et al.* (1942) found that an intense arterial spasm was the commonest cause of the limb ischæmia. There was no evidence of damage to the main arteries of the limb. The persistence of this spasm even after rapid liberation of the victim has been regarded as responsible for the subsequent muscle necrosis. According to Bywaters (1942), it is the autolysis of this dead muscle that determines the ultimate renal failure. A similar state of arterial spasm has occasionally been found to persist after tourniquet removal. Experimentally it has been found impossible to produce arterial spasm with the soft rubber tourniquet (Wilson & Roome, 1936), although Barnes & Trueta (1942) succeeded with a tight wire. The vessels were found uninjured, for the main artery of a limb, especially in the thigh, is well cushioned. Where the vessel in clinical tourniquet spasm has been exposed by operation, no vessel damage has been found. Further, this circumferential compression is not the type of stimulus that initiates arterial spasm, which requires a more brutal type of constriction.

The spasm appears to be best interpreted as a shock response, a reflex spasm, the reflex probably starting in the skin or deeper tissues and the sympathetic system serving as the efferent vasoconstrictor mechanism. It is probable that the reflex has to travel via the spinal cord, for experimentally the opposite limb vessel is also found involved in spasm. The appropriate treatment of this type of spasm is not yet decided. Hitherto, particularly in "crushing injuries," treatment has been concerned more with the saving of the life of the patient by attention to renal function, than with the limb. It had been hoped to prolong the vitality of the limb by keeping it cool, whilst waiting for the spasm to disappear spontaneously (Blalock & Duncan (1942) have shown experimentally that renal complications can be averted by cooling the limb). This type of spasm, however, appears to be particularly recalcitrant. Procaine injection of the major nerve trunks should be tried; both the afferent paths and the efferent sympathetic fibres will thus be blocked. Experimentally, sympathectomy has proved of definite worth.

General Condition and Spasm of Major Vessels

The generalised contracture of the smaller skin vessels in shock is well known, and is indicated by skin pallor. Studies of the effects of venesection (Barcroft, Edholm, McMichael & Sharpey-Schafer, 1944) show that with moderate hæmorrhage—800 cm.³—the flow of blood to the muscles remains fairly constant unless syncope supervenes, when vasodilatation in the muscles has been demonstrated. With more severe hæmorrhage, the major vessels have been found, experimentally and clinically, to be small and contracted. In states of shock other than hæmorrhagic, arterial spasm has at times become sufficiently marked to obliterate the distal pulse, affecting different limbs in turn. Even in the mild shocked case, "irritability" of the vessel is a particular feature, and with the slightest dissection around it the vessel contracts; this may be of special significance in the type of vascular spasm that follows injury to neighbouring tissues. There is also some evidence that vasoconstrictive shock may determine the onset of a Volkmann lesion (Shepherd, 1943). This rationing of blood to the limbs when the general condition is poor, has to be carefully remembered in the treatment of the limb with vascular spasm. Attention to the general condition must therefore be the first consideration.

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REVIEW OF SELECTED PAPERS

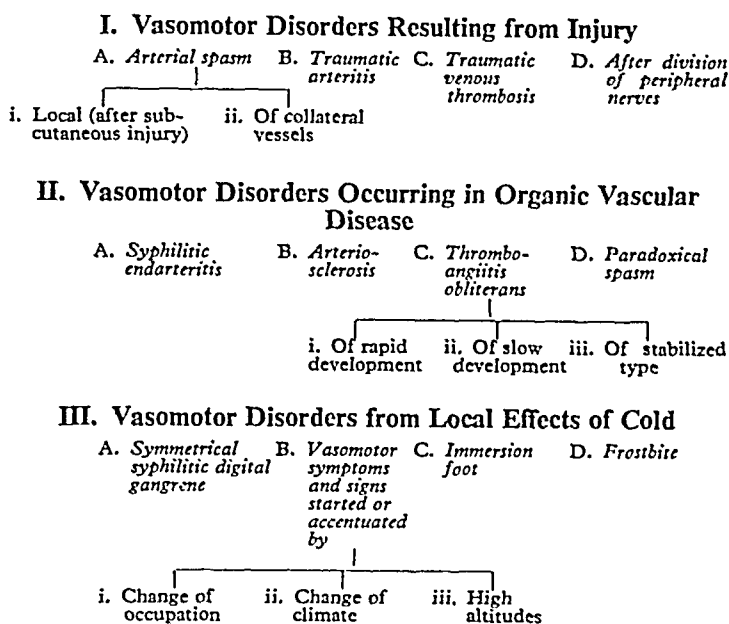
Peripheral Vascular Injuries

395

DISCUSSION ON IMMERSION INJURIES AND VASOMOTOR DISORDERS OF THE LIMBS IN WARTIME

by J. R. Learmonth, C. C. Ungley, W. Blackwood, J. B. Gaylor, R. Greene & T. Lewis, *Proceedings of the Royal Society of Medicine*, 36, 515-522, August 1943

Professor J. R. Learmonth said that in total war vasomotor disorders might affect all age-groups, and their effects were most serious in the elderly, in whom arteries had lost resilience. He suggested the following clinical classification:



Arterial spasm resulted from arterial injury; it was difficult to distinguish from arterial thrombosis. Both conditions might lead to vasoconstriction in collateral vessels. Spasm has been unaffected by periarterial sympathectomy proximal to the lesion, by attempts at reflex vasodilatation, and by preganglionic sympathectomy. The possibility of spasm or thrombosis was an urgent indication for exploration of the suspected artery, and excision of obviously injured segments. In the interval the nutrition of the limb should be conserved by avoiding the local application of heat, and possibly by the application of local cold. Uncomplicated arterial spasm recovered spontaneously.

Traumatic arteritis might occur in the main arteries of otherwise healthy young men, with resulting thrombosis. The clinical features were those of progressive ischaemia. These cases had been treated by preganglionic sympathectomy, followed by excision of the thrombosed segment of vessel in cases where this was feasible.

Traumatic venous thrombosis [or spasm] might give rise to reflex arterial constriction, which was relaxed by interrupting the appropriate preganglionic sympathetic fibres by paravertebral novocain injections.

In *organic vascular disease* the pathological diagnosis might be syphilis, arteriosclerosis, or thrombo-angiitis obliterans. The clinical features included both nutritional lesions and vasomotor attacks of the Raynaud type. In most cases treatment should be conservative; but in selected younger patients suffering from thrombo-angiitis, preganglionic sympathectomy might permit minor rather than major amputations.

Vasomotor disorders from local effects of cold included the rare condition of symmetrical syphilitic digital gangrene, and the numerically important group in which vasomotor symptoms and signs had been started or accentuated by change of occupation, change of climate, or exposure to the cold of high altitudes. Examples of the latter group were given. In general, operative treatment by preganglionic sympathectomy was employed only when it was desired to retain the patient in one of the Armed Services; otherwise treatment was conservative.

In *immersion foot*, first-aid should aim at preventing a too rapid return of blood-flow to the chilled parts; patients were

kept prone, by an open window, with the legs uncovered and elevated. In the later stages the attitude towards amputation should be rigidly conservative.

Surgeon Commander C. C. Ungley began by summarising the main clinical features of immersion foot, and described the three phases (prehyperaemic, hyperaemic and posthyperaemic) through which the extremities pass. Cases were classified into 4 groups according to the amount of sensory loss to cotton wool touches at 7-21 days after rescue:

- i. Minimal cases with no, or at most transient, interference with nerve function.
- ii. Mild cases with reversible nerve damage.
- iii. Moderately severe cases with irreversible (degenerative) nerve lesions.
- iv. Very severe cases with irreversible (degenerative) nerve lesions usually with gangrene.

A further subdivision into 9 smaller groups was also made. It was found that classification in this way correlated well with the severity of the other features of the condition, and a prognosis could be given for each group of cases.

Vasomotor observations in the hyperaemic and posthyperaemic stages were recorded. Serial observations of skin temperature showed that in moderately severe cases the digits of the affected extremities might remain warm (30-35° C.) for as long as 7-8 weeks after rescue. During this period the normal skin temperature gradient from groin to toes was abolished. In the later stages of the hyperaemic phase the temperature of the toes became unstable and they might be very warm one day and cold the next. In the early stages a vasomotor paralysis was present and the temperature of the toes remained unaltered at a high level despite immersion of the arms in cold and hot water. Later, as the toes cooled, normal vasomotor activity might be restored or abnormal vasomotor responses might be observed. It was demonstrated that during the hyperaemic phase the cutaneous vessels of the feet were sensitive to physiological concentrations of circulating adrenaline released by insulin hypoglycaemia. Skin-temperature observations made during experiments in fan-cooling proved the efficacy of this method of treatment in reducing the temperature of the hyperaemic feet and also yielded some interesting and curious results. The speaker pointed out that there was a certain similarity between the findings in the hyperaemic stage of immersion foot and those which follow postganglionic sympathectomy. In the late hyperaemic stage it was often found that, if the feet were exposed to cold (e.g. by fan-cooling), their temperature would remain low for a very long period and would rise only very gradually despite efforts to accelerate warming by raising the body temperature. This phenomenon of delayed warming persisted into the posthyperaemic state, where it became associated with that of cold-sensitivity, and attacks of the Raynaud phenomenon might be observed. It was thought that these phenomena were not entirely vascular in origin but might be the result of partial denervation or re-innervation of cutaneous blood vessels whereby they become sensitised to adrenaline and similar substances and to the local vasoconstrictor effect of cold.

Dr. W. Blackwood dealt with the pathological findings in clinical and experimental immersion foot, which suggested that "at the time of immersion damage was done to all the structures in the limb of a degree and to a level dependent upon the length and severity of exposure." Changes were patchy; axis cylinders and myelin sheaths were killed, muscles were damaged. After rescue, nerves began to regenerate; muscles were either re-innervated or replaced by fibrous tissue. [See also experimental observations of Blackwood & Russell, 1943.]

Dr. J. B. Gaylor said that in the cold-sensitive stage of immersion foot there was pathological failure of reflex vasodilatation, varying from lack of response to a slow rise, even when the toes were anaesthetic.

Dr. Raymond Greene considered that the Continental opinion that the sympathetic supply to the affected parts should be interrupted was not physiologically sound. In immersion foot, cold had performed a postganglionic sympathectomy; and only in the cold-sensitive state, when partial regeneration had occurred, should preganglionic sympathectomy be considered. In the acute phase, increased

arterial input would do harm by increasing transudation. [See also Greene, 1943.]

Sir Thomas Lewis emphasised that all available evidence indicated that cold, as cold, damaged the tissues of immersed limbs, and that the damage was the greater the longer the exposure and the greater the degree of cold. [See also Lewis, 1942.] Sympathectomy should be reserved for the rare late *algid* phase of the affection. The hypothesis that arteriectomy would release reflex constriction of collateral vessels had not yet received physiological sanction or proof.

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¹ [see BMB 398] ² [see BMB 402] ³ [see BMB 396]

Injury from Exposure to Low Temperature

396

SWELLING OF THE HUMAN LIMBS IN RESPONSE TO IMMERSION IN COLD WATER

by T. Lewis, *Clinical Science*, 4, 349–360, December 1942

Sir Thomas Lewis, Director of the Department of Clinical Research, *University College Hospital*, London, adds in the present paper to his well-known work on the physiology of the skin. After noticing that his hand became swollen during long immersion in cold water he proceeded to analyse experimentally the causes of the swelling. Observations were made chiefly on the author's own hands. The volume of the hand was measured by a displacement method. Before each measurement the veins were emptied by raising the arm for one minute, after which the circulation was stopped by throwing a pressure of 200 mm. Hg into a pneumatic cuff embracing the elbow joint with the fist clenched.

Three factors can contribute to such swelling—imbibition of water by the skin, engorgement of the smaller blood vessels, and oedema. At 35° C. swelling can be entirely prevented by enclosing the hand in a loose rubber glove and keeping the arm horizontal. In the absence of these precautions swelling occurs, and is due partly to imbibition by the skin and partly to engorgement of the small vessels and oedema due to mechanical causes.

At 5° C. there is little or no imbibition of water by the skin, but swelling may amount to an increase of as much as 15 % which is more than twice that at 35° C. If the arm is kept horizontal swelling is only slightly diminished at the lower temperature. The swollen hand shows typical oedema and pitting of the subcutaneous tissues. The oedema fluid contains about 3 % of protein, showing that there is increased permeability of the vessel walls.

From the evidence presented in this paper the author concludes that long exposure to temperatures of about 15° C. or lower directly injures the tissues and leads to the liberation of "H-substance," the mechanism believed to be common to cutaneous injuries, and the production of an inflammatory oedema. The author points out that if 60 cm.³ or more of albuminous fluid may be lost into a hand exposed to cold for 3 hours, it is clear that there must be a much greater loss of fluid and protein into the tissues when, for example, sailors are adrift in open and swamped boats, with larger areas of several limbs exposed for hours or even days. This factor should be taken into account in estimating the effects of exposure to cold upon the whole circulation.

397

PERIPHERAL VASONEUROPATHY AFTER CHILLING: "Immersion Foot and Immersion Hand"

by C. C. Ungley & W. Blackwood, *Lancet*, 2, 447–451, 17/10/42

This paper contains the first report on "immersion foot," a condition which was found to develop in men who had been exposed in open boats with their legs immersed in cold sea-water, and which closely resembled the "trench foot" of

the 1914–18 war. The hands may be similarly affected. Investigations on some 80 cases seen in Scotland over a period of 2½ years are described. In these cases immersion in sea-water at –2° C. to 10° C. for periods up to 14 days resulted in damage to peripheral vessels, nerves, muscles and skin.

The affected limbs usually passed through three main stages,* *prehyperæmic*, *hyperæmic* and *posthyperæmic*. Late sequels included recurrence of pain, tingling, swelling or blisters, persistence of a cold-sensitive state or of hyperhidrosis, and occasionally circulatory defects suggestive of vascular occlusion. Of 18 moderately severe cases which were followed for 2 years, 7 were doing full duty, 2 had been invalided, and the rest were doing light duty such as office work at the end of that period.

The paper concludes with a detailed discussion of the pathogenesis and general principles of treatment of the condition.

398

EXPERIMENTS IN THE STUDY OF IMMERSION FOOT by W. Blackwood & H. Russell, *Edinburgh Medical Journal*, 50, 385–398, July 1943

This important paper deals with the histological changes in muscle and nerve in the tails of rats, following prolonged immersion in cold (4°–5° C.) artificial sea water. Exposures of 48 hours produced slight lesions, of 96 hours marked lesions. The experiments were conducted in three series. In Series A the animals were allowed to recover slowly, spending the first 24 hours in an unheated (13·5° C.) room, before transference to the animal house (18° C.); in Series B, after removal from the cold water they were warmed rapidly for 30 minutes in shallow water at 29° C. before transference to the animal house; and in Series C they were heated for 3 hours in an incubator (37° C.) before transference.

In general, lesions were confined to muscle and nerve, being absent in skin, subcutaneous tissue, and blood vessels. In Series A, the histological findings in rats killed at varying intervals after exposure were as follows: In animals killed immediately after the longer exposures there was polychromatic staining of the muscle fibres, loss of striation, and coagulation of segments of myoplasm into hyaline masses lying inside the muscle tubes (giving an appearance suggesting Zenker's necrosis). At 2 days after exposure, severely damaged myoplasm had disintegrated, the sarcolemma nuclei appeared to increase in number, and there was a general reaction manifested by capillary congestion, and polymorph and monocyte infiltration. After 3 days' exposure, reaction was well advanced, and the damaged muscle fibres were replaced by cellular tubes containing sarcolemma nuclei, phagocytes and some cells in mitosis. The destruction of fibres in any one muscle bundle was irregular. After 14 days, hyaline aggregations of myoplasm had been removed and the narrowed muscle tubes contained only a strand of striated myoplasm. Sarcolemma nuclei were numerous and were in groups. At 30 days, muscle fibres were still small, sarcolemma nuclei numerous and prominent. At 60 days, the picture was still much the same as at 30. The authors point out that fibre atrophy and sarcolemma nuclear increase may also follow denervation. Tower (1935) has shown that this change is not apparent earlier than four weeks after denervation.

Damage to the nerves also was apparent in animals killed immediately after the longest exposures, although its extent did not become clear as rapidly as with muscles. Irregularity of myelin sheaths with swelling of Schwann cells and occasional discontinuity of a few fibres was followed in 1–2 days by the early stages of Wallerian degeneration. At 3 days, the reaction was fully established and the disintegration of myelin and axis cylinder material was obvious. At 14 days, some of the myelin debris was removed, the Schwann tubes were easily identified, and increased cellularity of the nerve bundles was apparent. At 4 weeks, globules of degenerate myelin were still seen within the Schwann tubes in the main nerves, and the small branches to muscles showed a diminution in the number of the myelinated fibres.

In Series B the changes were fundamentally the same, but were more intense at 3 days. After 4 weeks nerve damage was similar, but there was less residual damage in muscle.

In Series C the muscle and nerve damage at 3 and 30 days was comparable to that in Series A.

* [see BMB 392]

The authors consider that neither denervation of muscle, nor organic vascular obstruction, contribute to the histological appearances, and that cold in itself may be responsible for the injury to muscles and nerves. The changes in muscle may be due to the selective inactivation of enzymes, those requiring most oxygen being retarded first; at the same time, slow oxidation continues, and metabolites accumulate. In muscle, this leads to the accumulation of lactic acid, and myosin, the main constituent of muscle protein, is unstable on the acid side of neutrality.

The authors point out that the similarity in nature and degree of the histological appearances in their three series does not support the hypothesis that slow warming limits the severity of the lesions. The article is illustrated by a number of superb photomicrographs.

[The authors' findings that warming after rescue did not lead to any alteration in the histological picture, should—as indeed they intended—be accepted only for the tail of the rat and for the range of temperatures obtaining in their experiments. They make the statement that 28° C. "cannot be considered a true warming up process;" and in Series C the temperature of the incubator was below the body-temperature of rats.]

The clinical rule that in "immersion foot" the parts affected should not be locally heated (especially to temperatures above normal) is still valid.]

[see also BMB 394: B. Animal experiments]

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399

IMMERSION FOOT AND IMMERSION HAND (PERIPHERAL VASONEUROPATHY AFTER CHILLING)

by C. C. Ungley, *Bulletin of War Medicine*, 4, 61–65, October 1943

Immersion foot is a condition which follows prolonged exposure to degrees of cold insufficient to cause true frostbite. It may occur without actual immersion of the limbs, and the hands may be affected as well as the feet. Thus, as the author points out, the term "immersion foot" is a misnomer and "peripheral vasoneuropathy after chilling" is suggested as a more comprehensive and accurate. The condition is most often seen in shipwrecked mariners who spend long periods on rafts or in lifeboats with their feet almost continuously immersed, but it may be observed under any conditions in which extremities are exposed to cold and wet. The severity of the condition is found to depend chiefly upon duration of exposure and temperature. Other factors which may influence severity are clothing, particularly footwear (which affords some protection for short exposures but may later be dangerous if it constricts swollen limbs), immobility, sea-sickness, starvation, age and race.

During exposure, and for several hours after rescue, the affected extremities are cold, numb, swollen, pale, blue or mottled in appearance, and are pulseless (the prehyperæmic stage). Within a matter of hours there is an abrupt onset of hyperæmia. The extremities become hot and dry with full and bounding peripheral pulses. Colour-changes on elevation and dependency are striking, and indicate a very active cutaneous circulation. The amount of swelling usually increases during this phase, and blisters, petechiæ, ecchymoses and areas of superficial gangrene may appear. The appearance of the feet at this stage may be most alarming, but the amount of tissue loss is usually slight and deep gangrene is rare. Damage to peripheral nerves is manifest by subjective and objective sensory disorders, and by motor, vasomotor and sudomotor paralyses. Pain of a burning or shooting type may be severe and only relieved by morphine; in milder cases patients complain of tingling or pins and needles. These symptoms are related to warmth and dependency, and are alleviated by cooling and elevating the limbs. They increase in severity for the first 7–10 days after rescue and then gradually subside but may persist for as long as 6–10 weeks. Sensory loss of glove or slipper type for all varieties of sensation is often observed in severe cases. Hyperæsthesia is observed in milder cases, and, during the recovery phase, in cases with degenerative nerve lesions. Motor lesions consist of wasting, loss of power and impaired electrical reactions in the intrinsic muscles of hand or foot. Cutaneous vasodilatation, absence

of reflex vasomotor activity on heating and cooling unaffected limbs, and failure of the skin temperature of the digits to rise after peripheral nerve block are evidences of vasomotor paralysis.

It is pointed out, however, that all the vascular disturbances in the hyperæmic stage of immersion foot cannot be accounted for on the basis of paralysis of sympathetic vasoconstrictor fibres. Tests of sudomotor activity in this stage show areas of anhidrosis approximately corresponding to those of sensory loss. The duration of the hyperæmic phase varies from a few hours to 14 weeks or more, depending upon the severity of the case. It is succeeded by a posthyperæmic phase in which the extremities are permanently cool or cold, hypersensitive to exposure to cold, and sweat excessively, particularly in response to emotional or painful stimuli. In some cases an intermediate stage is observed. In this the extremities, although usually warm, if exposed to a low temperature may become very cold and remain so for many hours, only becoming warm again very slowly (algid state). This condition passes into the cold-sensitivity of the posthyperæmic stage, in which attacks of the Raynaud phenomenon may occur. The physiology of these late vascular disorders is as yet imperfectly understood.

Cases are graded according to the amount of nerve damage as assessed by the amount of sensory loss: (a) minimal, with little or no interference with nerve function; (b) mild, with reversible nerve damage but no blisters or gangrene; (c) moderate, with irreversible (degenerative) nerve lesions; (d) very severe, with irreversible (degenerative) nerve lesions and gangrene.

It is found that classification in this way can be correlated with the severity of the other features of the condition and that the prognosis can be assessed for each group.

In material obtained from cases of immersion foot, pathological changes have been observed in muscles, nerves, arteries and veins. It is not certain whether these changes are the direct result of cold, or are produced indirectly by ischæmia or other factors.

In regard to prevention, the instructions given by the Medical Research Council (1943) are quoted. For the immediate treatment of immersion foot, elevation of the affected limbs, which should remain exposed to the air, and the application of warmth to the body are recommended. Heating the affected limbs is condemned. In hospital, dry-cooling the limbs by fans or ice-bags has given good results, particularly as regards the relief of pain. Rest in bed until all swelling has subsided and the patient can walk without pain is advocated. In the presence of gangrene, cleanliness and an attitude of surgical conservatism are required. Sympathectomy has no place in the early treatment of immersion foot, but may be of value for the symptoms in the late post-hyperæmic phase.

REFERENCE

¹ Medical Research Council (1943) *War Memorandum No. 8: Guide to the preservation of life at sea after shipwreck*, London

¹ [see BMB 403]

400

ÆTIOLOGY OF "IMMERSION FOOT"

by B. W. Goldstone & H. V. Corbett, *British Medical Journal*, 1, 218–219, 12/2/44

The distinction between frostbite and chilling of the tissues is emphasised. The authors describe the clinical features seen in four parties of rescued men whose limbs were exposed to immersion in water above freezing point. A swollen stage and a stage of diminishing œdema are described. In the former the extremities are painless; in the latter there are severe pain, paræsthesiæ, tenderness of the feet with objective sensory loss; and the ankle jerks are stated to be diminished or absent. The resemblance of the picture to that of peripheral neuritis is stressed. Salt-water boils and duodenitis occurring in two cases (one fatal from hæmorrhage) are mentioned as complications.

It is considered that the clinical features of the immersion foot syndrome are the result of the combined effects of cold and relative ischæmia. In response to this double trauma the biologically weakest tissue, nerve, suffers first; hence the resemblance of the condition to peripheral neuritis. It is only if exposure is severe that the more resistant tissues suffer and gangrene results.

In contrast to current teaching, the authors believe that measures for active local vasodilatation have a definite place in the treatment of the syndrome, and state: "After the first few days of illness most of our patients were allowed a heat-cradle to their feet. When the pain became severe they begged for the cradle; it relieved the pain." They rightly stress the importance of the weakened neuro-muscular apparatus of the feet. Early weight-bearing is to be avoided and faradization and foot exercises are recommended.

[The authors do not appear to have differentiated between two distinct syndromes resulting from prolonged immersion of the extremities which have been described, the "peripheral vasoneuropathy after chilling" of Ungley & Blackwood (1942), and painful swollen feet secondary to prolonged dehydration and malnutrition (White, 1943). No details of the conditions of exposure are given, and it seems probable that many, if not all, of the present cases belong to the second group.]

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¹ [see BMB 397]

401

STUDIES IN THE PATHOLOGY OF HUMAN 'IMMERSION FOOT'

by W. Blackwood, *British Journal of Surgery*, 31, 329-350, April 1944

This is a histological study of material from 14 cases of immersion foot, consisting of a detailed and profusely illustrated account of the individual cases, with short clinical notes, followed by a consideration of the histological changes in the individual tissues.

The specimens varied in type from a digital nerve to a whole foot and leg; they varied also in the time which had elapsed between the period of exposure and the removal of the specimen; the earliest being a foot removed from a man who died during exposure, and the latest a lower limb amputated 26 months after exposure. In the later cases gangrene and chronic infection were sometimes present. Material was not obtained from cases during the early days following exposure.

"Blood vessels, muscles, nerve trunks and bone were particularly examined. The relative severity of injury to the tissues varied, being most severe in nerves and muscles." The proximal level of nerve and muscle injury was often far proximal to any areas of cutaneous necrosis.

Organic vascular changes were found to be minimal, except close to gangrenous extremities or in chronically infected stumps. There was no evidence that the cold-sensitive state, so often seen clinically, had a basis in organic arterial change.

Zenker's hyaline necrosis was seen in the foot muscles of a man who died during exposure. "Muscle was not seen again until 4 months after exposure. In the experimental animal (Blackwood & Russell, 1943) the early part of this interval was occupied by inflammatory changes in the necrotic muscle fibres, resulting in the production of slender hyper-nucleated fibres. It seems likely that a similar process occurs in man, but of this there is no histological proof." From 4 months onwards the changes were indistinguishable from those due to denervation, and were associated with severe degeneration of nerves to the muscles. From 12 months onwards there was evidence of re-innervation, and in some cases of restoration to normal. Fibrosis of muscle was not a prominent histological feature.

The nerves showed degeneration in all cases surviving exposure. In the later cases regeneration was present. Three cases allowed an estimation to be made of the rate of regeneration. This was slow but not unduly so. The nerve injury was often subtotal, and large myelinated fibres were amongst those surviving exposure. This feature, which was not specially noted by the author, suggests that the pathological process does not selectively attack the large myelinated fibres.

The bone: "In uninfected cases . . . there was new bone formation subperiosteally and around the haversian canals to a degree sufficient to reconstitute the radiographic normal."

The author has not discussed pathogenesis because of the lack of the very important evidence of very early post-

exposure material. As stated in the preamble, "The histological findings in this series of specimens tell part of the story of the bodily reactions to severe chilling of the extremities. Though the story is incomplete, it seemed advisable to put the findings on record in view of their present interest and because no other account of the histology of human immersion foot has been found."

[see also BMB 394: A. Human material]

REFERENCE

- ¹ Blackwood, W. & Russell, H. (1943) *Edinb. med. J.* 50, 385

¹ [see BMB 398]

402

THE IMMEDIATE VASCULAR CHANGES IN TRUE FROSTBITE

by R. Greene, *Journal of Pathology and Bacteriology*, 55, 259-267, July 1943

The author reviews previous studies on the effects of cold on the tissues, and reports the results of his own experiments on mice. The tails of the mice were frozen by means of solid carbon dioxide, at temperatures from -62° to -67°C . Tails thus frozen for 15 minutes invariably became completely gangrenous, and were shed 7 days later. Freezing for 5 minutes produced similar changes but the proximal inch [about 2.5 cm.] of the tail survived. Freezing for 1 minute at -62°C . was found to result in a constant sequence of events after the animal was removed from the freezing chamber; this was adopted as the procedure for most experiments, and is referred to as *standard frostbite*.

Macroscopic changes in standard frostbite. Immediately after freezing the tail is pale and hard; thawing is complete in 10 minutes and is associated with hyperæmia and slight œdema. No correlation was found between the amount of œdema at this stage and the ultimate result. Hyperæmia subsides in 5 hours; 24 hours later the terminal centimetre of the tail is brownish purple, gradually undergoes dry gangrene, and is shed at any time up to 18 days.

Microscopic changes. Apart from constriction of the caudal artery, vascular changes were confined to the portion of the tail destined to become gangrenous, in which swelling of the vascular endothelium and the formation within the lumen of the vessel of a shrunken pigmented mass consisting of clumps of erythrocytes were constantly observed. These changes were present 5 minutes after freezing. Later, there was further intimal damage and the development of signs of necrosis of the tissues of the tip of the tail, which continued up to the time of separation. In tails frozen for 2, 5 and 15 minutes the changes differed only in their intensity from those in standard frostbite. The author points out the significant fact that arterial thrombosis was not observed in any instance. The essential change is a loss of fluid through damaged vascular endothelium leading to an accumulation of erythrocytes in the blood vessels. True thrombosis may occur as a secondary phenomenon. These findings are in accordance with those observed by Rotnes & Kreyberg (1932).

The author's view is that little permanent damage is done to tissues as a result of exposure to degrees of cold less than that necessary to cause solidification, but that considerable damage may result from the events which occur during warming. In true frostbite, the tissues undoubtedly suffer damage from the direct effects of cold. The exact nature of the pathological changes which occur is imperfectly understood. From the point of view of treatment it is obviously desirable to have a clear picture of the changes which take place in the blood vessels of an extremity exposed to severe cold.

REFERENCE

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403

A GUIDE TO THE PRESERVATION OF LIFE AT SEA AFTER SHIPWRECK

Medical Research Council: M.R.C. War Memorandum No. 8, London, 1943

In October 1941, the *Medical Research Council*, at the request of the medical department of the Royal Navy, appointed a

Committee on the Care of Shipwrecked Personnel. The task of the Committee was to examine conditions of exposure after shipwreck, with special reference to water requirements, extremes of temperature, food requirements and stimulants.

The Committee's recommendations are embodied in this Memorandum, which is written in simple language and is full of practical and authoritative information. Under "Lifeboat ailments," the essential features of frostbite and immersion foot and their prevention are summarized. The treatment of these conditions is outlined under "Treatment after rescue." Although this Memorandum is noted here because of its references to the effects of exposure to low temperatures, these references are only a small part of the subject matter.

404

PREVENTION AND TREATMENT OF IMMERSION FOOT AND OF FROSTBITE

Ministry of War Transport, *Notice No. M. 226*, London

The following is the text of instructions in a leaflet issued to British mariners. It is recommended that all officers and men should read them carefully, and that copies should be kept in lifeboats.

Immersion Foot

When the feet or legs are immersed for many hours in water (fresh water, salt water or liquid mud), at low temperatures (temperatures measuring 15° C. (59° F.) or lower) the skin and underlying tissues very gradually suffer damage, which is the greater the colder the water and the longer the immersion. Sea water sufficiently cold to injure is usual in the Atlantic (winter and summer) from latitude 50° northwards.

Signs. Immersion in water cold enough to damage is painful, but this pain is not usually severe and soon lessens. In half an hour the immersed part of the limb is red and numb and power in it is reduced. This numbness and weakness get worse, and in 3 hours the limb is a little swollen. The swelling increases with time, especially if the limb is hanging down. All these early signs of damage quickly disappear if immersion ends and the limb can be warmed (warming must be very gradual—see "Treatment" below). Signs of damage are more persistent and more serious after immersion has lasted for several days; in such cases blisters or dark patches may appear on the skin and the skin may become broken. Only after long exposure in very cold water is recovery incomplete.

Prevention. Make all efforts to avoid those discomforts and disabilities which may lead to the risk of more permanent damage. The damage comes out of coldness, and the chief source of coldness in boats is cold water. Avoid contact with water as far as you can. Keep your feet out of water by keeping the bottom of the boat as dry as possible or by raising the feet. Even if you are wearing sea-boots the less water touches these boots the better; cold from the water will come through them. If your socks have become wet, wring them out, empty your boots and put them on again quickly; if you carry dry socks put these on rather than the damp ones. Try frequently moving your feet and toes. Unless the sun is out do not bare your feet to rub them; the exposure to the air will cool your feet more than the rubbing will warm them. If you rub them do it very gently. Rubbing the skin when it has become swollen, numb or tender, will do more harm than good. Greasing the feet is not much use. Keeping the upper parts of the body dry and warm is extremely important, because it also helps to keep the limbs warm. It is better to keep damp or wet clothes on the body under water-proof covering than to strip and wring out the clothes in a cold wind. Do not wear tight garters, boots or any tight clothing on the legs.

Treatment. Treatment will begin at once after rescue from boat or raft. Lift the patient on board; remove all clothes from the body, and wrap the body in warm blankets. Hot bottles may be placed against the body between the blankets, but none should be allowed to come near the affected limbs. These limbs should be handled only very gently and protected from the weight of bed clothes; and they should be kept cool, if necessary by exposure to the air; heating them in any way is harmful. The patient should be kept in bed with feet raised on pillows and cool until all swelling has gone, and subsequently until he is able to walk without pain, or until he comes under medical supervision. Blisters, open sores or darkened areas of skin should be dusted with sulphanilamide powder and kept covered by clean dry clothes, which are to be removed gently and renewed if they become stained; the part should be kept quite dry and no lotions, ointments or antiseptic except the powder above recommended applied.

Frostbite

True frostbite is a condition in which the skin and sometimes deeper tissue becomes actually frozen. The damage is not caused

directly by cold, but by minute crystals of ice which form within the skin. Frostbite only occurs on land when the ground is hard frozen, or covered with dry snow or ice. At sea it occurs very rarely unless the sea water is freezing. Frostbite is almost unknown unless the temperature of the air is as low as -10° C. (14° F.), and is very frequent only if the temperature is much lower (-25° to -30° C. or -13° to -22° F.). Wind encourages and sunlight discourages frostbite at a given temperature.

Frostbite affects uncovered parts of the skin; fingers, ears and nose when exposed are most prone to freeze and in this order. It affects parts that come in contact with very cold substances—the feet with ice or frozen ground, the fingers or mouth with cold metal.

Signs. When skin freezes it usually becomes pale, the colour is yellowish-white, it looks unusually opaque, it becomes of wooden hardness; this hardness is the only completely reliable and invariable sign of freezing. The patch of skin so affected is usually clearly marked off from the rest, both to sight and touch. The freezing usually happens in skin that is already tingling or numb with cold. The actual freezing occurs quite suddenly, sometimes after a sudden abrupt stinging pain or local pricking; it is also very apt to pass unnoticed. The frozen patch will enlarge if untreated, but the subject will not feel this. Skin once frozen remains quite unchanged until it thaws; it will then react by a more or less violent inflammation, according to the extent and hardness of the freezing.

Reaction. Directly after thawing the skin becomes bright red and hot. A short freeze is followed by itching and whealing of the skin, which disappears within a few hours; a severe freeze causes death of the skin which comes away after blackening and leaves a hole (or ulcer) in the skin; a very severe and extensive freeze will cause the death and consequent gangrene of the end of the limb affected (usually the toes).

Prevention. Frostbite is avoided by keeping warm. In intense cold the clothing should be windproof and abundant; thick gloves and ear protectors should be worn. Food should be abundant, fat and hot. The man should be in constant movement when out of doors; the feet especially should never be still for long. The socks should be thick and always dry. Cramped positions should be avoided. There should be no tight clothing on the limbs. Metals should not be touched with bare skin or with the mouth.

The feet and all exposed skin should be kept greasy, by gently smearing the parts with oil (as supplied in ships making Arctic voyages and in all life-boats and emergency life-rafts) or vaseline and by refraining from washing frequently.

Beard and moustache should be clipped short or shaved away; icicles will form on untrimmed beard from the moisture of the breath. When passing water the penis should be shielded from wind and afterwards carefully dried.

Men out of doors together should watch each others' faces for the first appearance of patches of frost; early freezing can be detected by the man himself by wrinkling the face to find areas of stiffness. Any frozen area should be thawed at once by placing a bare warm hand on it.

Treatment. Small frozen areas may be thawed rapidly by covering them with a warm hand; they require no subsequent treatment.

Larger and more severe freezes, as when a whole foot is involved, should be thawed by placing the limb inside a companion's clothes. Rubbing with snow is dangerous. If it is possible, the part should be thawed by immersing it in tepid or cooler water. On thawing, the skin will at once soften and will quickly become pink or red. If pain is severe on thawing, cool the part a little with water, or by short contacts with snow. It is important that after thawing warming up should be very gradual; application to the affected part of hot water or bottles or exposure before fire is dangerous.

Keep the part subsequently at absolute rest, the body well fed and warm, but the damaged part relatively cool. Put a light clean dressing, such as a wound dressing, over the damaged part and bandage very lightly; the object is as much to protect the part as to keep it clean. If there are any blisters or broken skin powder them with sulphanilamide powder before applying the dressing. Blisters should not be opened unless a pair of perfectly clean scissors is available, which should preferably be dipped in boiling water before use.

It is to be noted that in frostbite the amount of dead skin and tissue that eventually separates away is generally much less than at first might seem possible.

Treatment by Low Temperature

405

COLD IN THE TREATMENT OF DAMAGE DUE TO COLD

by R. Greene, *Lancet*, 2, 695-697, 12/12/42

The author of this paper, who is at present a physician in the *Emergency Medical Service*, has gained a special experience

of his subject in the course of expeditions to Mount Everest in which he has participated.

In true frostbite no treatment can save the affected tissue, the death of which is inevitable owing to blockage of the vessels by corpuscles left stranded therein by excessive transudation. On the other hand, in the state of physiological reaction in which tissues are responding normally to damage by cold, treatment is unnecessary. Frequently, however, as in immersion foot and trench foot, the tissues are merely chilled, in which state they are endangered by congestion resulting from a lesser degree of transudation than in true frost bite.

It is traditional that warmth greater than that of the human body is harmful in the treatment of the state of chilling. Smith, Ritchie & Dawson (1915) showed that, when damage by cold has occurred, water at only 37° C. causes rapid œdema or a rapid increase in œdema already present, an observation confirmed by Lewis & Love (1926). A previous investigation (1941) on mice by the present author demonstrated that frost-bitten parts must be kept cool. Lake (1917) has shown that the survival rate of tissue-cultures is greatest between - 5° C. and + 5° C., while Lambert (1913) found that embryonic chick tissues survived best at + 5° C. Allen (1939) has shown that tissue necrosis after ligation of a limb is increased by heat and diminished by cold. In the author's opinion, all these findings lead to the conclusion that the frostbitten or chilled limb should be kept at a temperature just above freezing point, and he has accordingly designed a portable refrigerator (the Greene-Simpson Frostbite Cabinet), with the aim of testing the practical truth of this theory in the treatment of conditions such as immersion foot.

The cabinet consists of an upper and lower compartment. In the upper compartment is a metal tray in which two blocks of solid carbon dioxide (total weight 10-12 pounds) [about 4.5 to 5.5 kg.] are placed, each block wrapped in a separate canvas bag. The lower compartment opens in two sections, and has two padded apertures for the patient's feet, which are placed in position with sufficient cotton wool or bandage round the ankles to fill up the padded entrance holes when the cabinet front is replaced. If the cabinet is required for one limb only, the other hole must be completely plugged with cotton wool or bandage to prevent leakage of air. This lower compartment also contains a thermometer which registers on a dial at the back of the cabinet. Air circulates through two flues between the compartments. These flues are controlled by knobs at the back, by the manipulation of which the desired temperature can be maintained. When the refrigerant has evaporated to 2-3 pounds [about 1 to 1.5 kg.] it is removed from the bags and placed directly in the metal tray. The cabinet requires 8-10 pounds of refrigerant every 24 hours.

The author has not had the opportunity of fully testing the efficacy of this method of treatment, but suggests that, in the first instance, experiments should be controlled by treating only one limb in patients who are bilaterally afflicted.

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406

TREATMENT OF IMMERSION FOOT BY DRY COOLING

by C. C. Ungley, *Lancet*, 1, 681-682, 29/5/43

Since a previous report (Ungley & Blackwood, 1942), in which the condition was described in detail, the author has had the opportunity to try out methods of dry cooling in the hyperæmic stage of "immersion foot" in 2 men, A and B, exposed for 34 hours on a raft in the North Sea. In case A attempts were made to relieve pain on the 15th day after rescue, by cooling the feet by means of a therapeutic refrigerator. This refrigerator was constructed on the lines described by Greene (1942), but made from wood instead of metal and not specially insulated. In spite of a good supply of solid CO₂ in the upper chamber and wide open flues, the temperature in the lower chamber of the refrigerator

varied in accordance with fluctuations in room temperature, and the patient's left great toe, which had been cooled from 30° C. to 24° C. during the first 75 minutes, had warmed by the next morning to 25.5° C. and ultimately to 27.5° C. Pains were less frequent and less severe than on the previous night, but the patient experienced considerable discomfort through being unable to move his legs. For this reason it was decided that, although efficient cooling could doubtless be maintained by such a cooling cabinet if its walls were suitably insulated, cooling of the feet should now be attempted by means of an electric fan.

The patient was transferred on the 16th day to a cabin with a temperature of 15° C., and covered with blankets except for his feet. Exposed thus for an hour, the feet remained hot (great toes 31°-32° C.), pains were severe, and the feet often twitched. An electric fan at full speed 12 inches [about 30 cm.] from the soles cooled the toes in 2 minutes to 23.7° C., and in 80 minutes to 18.6° C. and 20° C. During the next 3 hours, with the fan at reduced speed and at a greater distance, the temperature of the great toes was maintained in the region of 17° C. and the dorsum of the feet at 22°-25° C. Pain and tingling ceased within 5 minutes of starting the fan, and returned whenever the fan was turned off and the feet became warm again. Cooling below 21° C. was liable to cause considerable discomfort and efforts were subsequently made to adjust the speed and distance of the fan so that the temperature of the feet was not reduced below 23° C.

In case B, during exposure of the unclothed body on the 13th day after rescue to a room temperature of 18° C. for 80 minutes, the left foot cooled satisfactorily, while the right remained hot (great toe 30.5° C.). The cold left foot showed a normal vasodilator response when heat was applied to the trunk. Aching and stabbing pains on the nights of the 14th and 15th days, chiefly in the right foot, were promptly relieved on the 16th day by cooling the right foot with a fan. From the 18th to the 23rd day the left foot cooled normally during exposure of the unclothed body to a room temperature of 17.1°-17.8° C. The right foot, however, cooled only under the influence of the fan, but did not immediately warm up again when the fan was switched off, which suggests that the skin vessels of this foot were beginning to regain tone. By the 27th day both feet cooled normally on exposure.

These observations confirm the findings of Webster, Woolhouse & Johnston (1942) that cooling the hot limbs relieves pain and tingling. In severe cases, however, Webster and his colleagues found that premature removal of ice-bags was followed by marked increase of œdema, extravasation of blood and spread of gangrene, clearly indicating the necessity, in such cases, for continuous cooling. In the present author's cases treatment was not begun until œdema had subsided, no exudation or necrosis followed interruption of cooling, and return to high skin temperatures was not necessarily associated with immediate return of pains and tingling. In such circumstances intermittent fan treatment in addition to exposure of the uncovered feet to room temperature would be used. Greene's refrigerator might, it is suggested, prove useful for severe cases requiring long uninterrupted cooling, and not intolerant to restriction of leg movements.

The author concludes that the mode of action of dry cooling requires further investigation, and points out that it has yet to be determined whether long cooling will influence the rate of recovery of the peripheral nerve lesions.

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¹ [see *BMB* 405] ² [see *BMB* 397]

407

SOME USES FOR DRY COLD THERAPY, AND A PROPOSED COOLING CABINET

by W. G. Bigelow & E. C. G. Lanyon, *British Medical Journal*, 1, 215-217, 12/2/44

The authors discuss the value of cold as a therapeutic measure and describe a form of cooling cabinet which may be used for its application. The cooling system consists of a cabinet which is cooled by cold brine circulating through coils in the

wall. The brine is cooled in a separate refrigerating machine and pumped to the cabinet. Several cabinets may be supplied from the one refrigerator, and it is claimed that the whole unit can be made in a mobile form suitable for the needs of an army in the field. The authors consider that in military surgery cold therapy may be of value in four sets of conditions :

- i. *Frostbite and immersion foot.* Cooling of the extremities in the immediate post-exposure period is advised. Over a period of days the temperature of the cabinet is then gradually raised towards room temperature. The rationale of this treatment is the maintenance of a balance between local metabolism and the available blood supply.
- ii. *Wounds of extremities with impaired blood supply.* The rationale of cold therapy is as above. Cold may also relieve pain and inhibit bacterial infection. Very low temperatures need not be used, and any tendency to vasospasm in the cooled limbs may be overcome by reflex vasodilatation, sympathetic block or vasodilator drugs.
- iii. *Traumatic arterial spasm.* Refrigeration of the affected limb may be used as an adjunct to operative treatment (exposure of the affected vessel with or without arteriectomy), or as a form of conservative treatment to tide the limb over the critical period before a collateral circulation develops.
- iv. *Peripheral embolism.* Cooling reduces tissue metabolism and allows the tissues to survive until the associated vasospasm is released and a collateral circulation is established.

Nervous Control of Peripheral Circulation

408

THE MECHANISM OF THE VASOMOTOR REFLEXES PRODUCED BY STIMULATING MAMMALIAN SENSORY NERVES

by G. Gordon, *Journal of Physiology*, 102, 95-107, June 1943

Stimulation of the cut central end of mixed nerves may produce a rise or a fall in general blood pressure according to the characteristics of the excitation. The author examined this phenomenon in decerebrate or anaesthetised cats, employing an electrical stimulus which could be quantitatively graded with respect to intensity, duration, and frequency of repetition. Full details of technique and results are given.

Using a stimulus (condenser discharge) with time-constant of one millisecond and frequency of three per second, the sign of the vasomotor response depends on the amplitude of the stimulus; peak amplitudes below 12 volts produce a blood-pressure fall, and amplitudes of the order of 28 volts produce a rise of blood pressure under the same conditions.

When the shock-duration is reduced to 0.1 millisecond, no pressor effect can be obtained even at 80 volts amplitude with frequencies below 100 per second.

There is, however, a tendency to produce pressor effects with frequencies of over 100 per second with shock configurations which at lower frequencies produce depressor reflexes only.

With certain stimulus-durations, therefore, either increase of amplitude or of frequency is found to reverse the vasomotor response, and the higher intensity or frequency is required for the pressor activity. The observations are altered in magnitude of response only, and not in kind, by section of the vagus or destruction of the nervous connections of the carotid sinus.

The author examined the peripheral mechanism of this differential sensitivity of the afferent side of the reflex by blocking the nerve proximal to the cut end with cocaine, cold, and asphyxia in turn.

He found that suitable doses of cocaine, which is known to act first upon the smallest fibres in a mixed nerve, abolish the pressor reflex while leaving the depressor activity; when asphyxia by arterial occlusion is applied to the preparation, the depressor reflex is abolished first, and may leave the pressure-raising action enhanced; asphyxia has been shown to act primarily upon the large diameter fibres. The effect of cold is similar to that of asphyxia.

The author concludes that the reflexes are mediated by different sets of afferent fibres, and that the pressor reflex with the characteristics of relative inexcitability to stimulation and ready inactivation by cocaine may be initiated through the C group of fibres.*

The author comments briefly on the possible importance of this differential vasomotor activity in connection with primary and secondary shock.

409

NOTE ON THE SPINAL ORIGIN OF VASOCONSTRICTOR FIBRES TO THE ARM IN MAN

by J. R. Learmonth & R. L. Richards, *Quarterly Journal of Experimental Physiology*, 32, 87-88, May 1943

In this brief communication the authors report, from the Department of Surgery of Edinburgh University, observations made on the vasomotor responses of the right hand of a male patient aged 19, in whom the anterior nerve roots on the right side were divided from the fifth cervical to the second thoracic segments inclusive. This operation was performed on 12/10/42 for the relief of gross athetosis of the right arm and shoulder due to a spastic right hemiplegia dating from birth.

"After operation the forequarter was completely paralysed with the possible exception of the rhomboids. It was not easy to be sure of this, because the shoulder girdle was still moved involuntarily, but much less violently, by the trapezius. Sensation was unimpaired save for some hypaesthesia in the second thoracic segment.

Vasomotor responses. On 25th November 1942 the patient was placed in a cool room. Thermocouples were attached to the left middle finger (control), and to the right little finger, right middle finger, and right thumb, and readings of skin temperature were taken at intervals of 3 minutes. At 23 minutes the feet and legs were immersed in water at 45° C. At 39 minutes the skin temperatures of the fingers began to rise, the rate of rise being nearly the same on both sides; the temperatures reached were somewhat higher on the left side. At 60 minutes the following temperatures were recorded on the right (paralysed) side: thumb 32° C., index 34° C., middle 34.5° C., ring 34° C., little 34° C. It was noted that the ulnar side of the right hand felt warmer than the radial side; the thermocouples were transferred to the thenar and hypothenar eminences, and to the wrists. The clinical impression was confirmed by the following readings:

	Right	Left
Thenar eminence . . .	23.5° C.	32° C.
Hypothenar eminence . . .	34° C.	34.5° C.
Wrist . . .	24.5° C.	31° C.

The observations show that, in this patient, reflex vasomotor response in an arm was normal, when the most cranial source of its preganglionic vasoconstrictor fibres was the third thoracic segment of the spinal cord."

410

VASOMOTOR DISTURBANCES IN THE HAND AFTER INJURIES OF PERIPHERAL NERVES

by R. L. Richards, *Edinburgh Medical Journal*, 50, 449-468, August 1943

Cutaneous vasomotor disorders after injuries of peripheral nerves are in part due to the interruption of sympathetic vasomotor fibres and in part due to disuse and therm-anaesthesia as a result of division of motor and sensory fibres. Previous work has shown that all the effects of nerve division can be attributed to interruption of motor, sensory and autonomic fibres, and that there is no need to postulate a separate set of fibres which exert a "trophic" influence on the skin and its appendages. Sympathetic vasomotor fibres to the limbs have a predominantly peripheral distribution, and in the upper limb most of these fibres are in the median and ulnar nerves. Vasomotor disturbances are therefore pronounced

* [Erlanger, J. & Gasser, H. S. (*Amer. J. Physiol.* 1930, 92, 43) classify the fibres of somatic nerves as belonging to groups A, B and C, according to their conductivity and irritability as demonstrated by the study of action potentials. C fibres have the slowest conduction rate.]

after division of these nerves, but are slight after division of cutaneous nerves to the more proximal parts of the limb or the radial nerve. In the present study, observations of vasomotor activity were made by recording skin temperature with thermocouples attached to a sensitive galvanometer. Only cases of complete division of the main nerve trunks of the arms are considered.

Immediately after nerve division there is a period of vasodilatation during which the denervated area of skin is hot, dry and flushed (the warm phase). This phase is attributed to the division of postganglionic vasoconstrictor neurons of the sympathetic system running in the peripheral nerves. The duration of this phase is variable, but is usually of the order of 21 days. It is succeeded by a phase in which the temperature of the denervated area is dependent upon that of its environment. Since the latter is usually low, this second phase may be referred to as the cold phase, and is permanent unless the divided nerve be repaired. The change from warm phase to cold phase is gradual and the factors responsible for the change are as yet imperfectly understood. It is believed that (a) sensitisation of denervated cutaneous blood vessels to circulating adrenalin, (b) degeneration of sensory fibres responsible for the local "axon reflex" (which according to Sir Thomas Lewis is so important in maintaining the temperature and nutrition of the normal digit), and (c) a lowered local metabolism in the denervated area are all important factors, but probably do not contain the full explanation of the later changes. The possibility that changes take place in the blood vessels, and particularly the arteriovenous anastomoses, cannot be excluded.

In addition to studying the resting vasomotor state of denervated areas, the author made observations on reflex vasomotor activity. He discusses the physiology of the vasodilatation and vasoconstriction which occur in the contralateral limbs when the legs or arms are warmed or cooled, and postulates that the afferent pathway for the reflex may be either through nervous channels or by the action of warmed blood upon a central thermo-sensitive vasomotor centre. On the efferent side the precise nature of the peripheral mechanism responsible for the rapid vasodilatation which takes place in a normal limb is not certain. Release of normal vasoconstrictor tone with opening of arteriovenous anastomoses is partly responsible, but it is suggested that the response may be initiated through vasodilator fibres.

In a limb which is the site of a peripheral nerve lesion, it is found that denervated digits show a profound disturbance of reflex vasomotor activity whether they are in the early warm phase or the later cold phase. A completely denervated digit will fail to show any response. A digit which is partly denervated (e.g. the ring finger in most lesions of the ulnar nerve) may show an almost normal response. The responses are rarely clearly defined, and no two lesions of the same nerve will give identical results. It is often found that a denervated digit which is adjacent to a normally innervated area (e.g. the middle finger in most lesions of the median nerve) may show a delayed and gradual rise in temperature. This is probably not due to true reflex vasomotor activity, but is an indirect result of the vasodilatation in the adjacent normal area. This raises local metabolism; vasodilator metabolites are produced, and, as the initial blood flow of the denervated digit is low, metabolites accumulate and are destroyed or removed slowly, thus causing delayed and gradual vasomotor responses. It is unlikely also that the nerve supply of deeper blood vessels corresponds to cutaneous sensory territories, and dilatation of these will result in a greater blood flow to digits adjacent to areas with normal innervation.

411

REFLEX VASODILATATION IN SURGERY

by J. R. Learmonth, *Edinburgh Medical Journal*, 50, 140-154, March 1943

The author of this paper, who is Professor of Surgery at Edinburgh University, points out that the amount of blood reaching the part is an important factor in the management of many surgical conditions.

The rate of flow of blood through a limb may be varied in accordance with (a) the general needs of the body, and (b) the local activity of the tissues. When one limb is heated by

immersion in hot water, or by a hot air bath, heat is absorbed by the blood in the heated limb. Because of the local high temperature the metabolic rate of the tissues increases, thus further heating the blood through the limb. In order to maintain an even body temperature this extra heat has to be dissipated. This is effected by reflex vasodilatation of the vessels in the unheated part of the body, thus increasing the rate of blood flow in the unheated area.

The value of a method which can ensure a maximal blood supply in surgical conditions affecting the extremities needs no emphasis. These conditions fall naturally into 2 groups :

- (i) *Infected wounds* : There is an obvious need for a maximal blood supply to promote rapid healing, to combat infection already present, and to prevent the spread of subsequent infection.
- (ii) *Conditions in which the arterial channels are constricted or obstructed because of local vascular disease or dysfunction* : The need here is to ensure a blood supply adequate for the needs of the tissues, and thus to prevent tissue death.

There are two methods of using heat to increase blood supply : (a) local heating, and (b) reflex vasodilatation. In the first group of conditions, local heating can be used with impunity when the blood supply to the part is unimpaired. The local vasodilatation and the increased metabolic rate of the heated tissues induce a great increase in blood flow, because the arterial tree can dilate easily. In the second group of conditions, when the arterial tree is the seat of disease—e.g. arteriosclerosis—and the state of nutrition of the part is already precarious, local heating does not produce an increase in blood flow. As the local heating causes tissue metabolism to increase, the final state is worse because the tissues now become relatively ischaemic and local tissue death is brought nearer.

When reflex dilatation is used as a means of increasing blood supply in a diseased limb, there is no great increase in the tissue metabolism in the affected limb but the vessels will dilate to their maximum possible calibre. Local cooling of the affected limb is to be avoided (to prevent vasoconstriction) and equally the limb must not be allowed to create for itself a hot environment. If this were to occur, it would be equivalent to direct heating of the part. Frequent wiping to remove sweat, and the absence of dressings, help to conserve heat without overheating.

The method of reflex dilatation has been used with success in opening up collateral channels in cases of local injury to a main vessel (section, contusion, or spasm) or of thrombosis or embolism. In the sclerotic conditions of arteries the method can be employed with a measure of success which is dependent on the degree of sclerosis. It can often improve the blood flow sufficiently to avert or limit the extent of gangrene.

The condition of the nerves to the affected limb is of major importance. The final distribution of the vasoconstrictor nerves corresponds closely to that of the cutaneous nerves. Reflex vasodilatation cannot be effected in the area of supply of a divided peripheral nerve. Leriche (1939) has shown that a local lesion of a main artery (contusion or spasm) may impose a reflex vasoconstriction of its branches. Removal of the local lesion by excision is followed by an effective response to heating of a distant extremity. This effect is due to the interruption of the efferent vasoconstrictor nerve fibres when the artery is resected. Absence of response to reflex vasodilatation, in cases of wounding to an extremity in young individuals, justifies exploration of the wound to determine the state of the main vessel and, if this is found to be contused, excision of the affected segment.

The conditions in which reflex vasodilatation is of practical value are :

- (1) In organic vascular disease in which gangrene threatens, and in patients who have had a limited removal of gangrenous tissue.
- (2) In embolism of a main artery to secure, after initial spasm of the main vessel has disappeared, that collateral circulation will be maximal.
- (3) After ligation for aneurysm to compensate for temporary circulatory deficiency. In the extremities, sympathectomy should precede operations on the aneurysm.

- (4) In infective conditions of the hand or foot, after drainage has been established and fever is absent, to secure an extra blood supply for better heating and function.
- (5) In ulcers of the extremities.
- (6) After skin grafting, to increase the percentage of successful grafts.
- (7) After tendon repair in hand wounds.

The response to the treatment may vary widely from patient to patient, but reflex vasodilatation in the above conditions will in some save life and in others a limb.

REFERENCE

Leriche, R. (1939) *The surgery of pain*, London

412

SYMPATHECTOMY IN TREATMENT OF THE CRYOPATHIES

by E. D. Telford, *British Medical Journal*, 2, 360, 18/9/43

The author states that in 5 cases he has treated the late results of injury from cold by preganglionic sympathectomy. Four of these had suffered from frostbite; one from immersion foot. In one case of frostbite, the patient was unable to work after 18 months because of chronic painful ulceration in the hands associated with Raynaud's phenomenon. After bilateral preganglionic section of the cervico-dorsal chain, the ulcers healed and the attacks of vasospasm were much reduced in frequency and severity. This patient has remained well. In another case, 8 months after suffering from immersion foot the patient was unable to walk and complained of constant burning pain in the feet, which were tender and sweated excessively. The toes had been partly shed and the stumps were ulcerated. After bilateral lumbar cord ganglionectomy the pain was immediately relieved and the ulcers healed rapidly.

In the lower limb, Telford prefers spinal anaesthesia as the pre-operative test in order to determine the possibility of vasodilatation, and states that if in such cases it produces a rise of 1° C., sympathectomy is justified. In the upper limb when all the fingers are affected he employs nerve block of the ulnar nerve at the elbow.

Ischaemia

413

LOCALISED ARTERIAL THROMBOSIS OF INDETERMINATE ORIGIN

by J. R. Learmonth, W. Blackwood & R. L. Richards, *Edinburgh Medical Journal*, 51, 1-20, January 1944

In this paper are described 4 cases of localised arterial thrombosis occurring in the limbs of otherwise healthy young adults. In one the brachial was the artery affected, in the other 3 the femoral. Trauma is considered to be the most likely precipitating factor, although in only one case was there a definite history of injury, and that at a site distant from the thrombosis; in the other 3 cases it is possible that an injury passed unnoticed.

The cases presented the cardinal features of ischaemia, still not readily enough recognised. Pain was a complaint of all 4, and a prominent feature of the brachial artery case in whom it was severe in the wrist and hand, and ultimately relieved only by morphia; it had been present for a year before nutritional lesions appeared. When the lower limbs were affected, the pain of intermittent claudication was experienced, and also distant pain in the peripheral territory of the blocked vessel, aggravated by exercise and felt severely at night. Other subjective symptoms were paresthesiae and a sensation of coldness of the extremity affected. Nutritional lesions (gangrene of an index finger and a perforating ulcer on the sole of the foot) had occurred in 2 cases before they came under observation; in the other 2, claudication and weakness of the affected limb were the presenting symptoms.

Diagnosis is dependent on clinical examination of the limb, the response to reflex vasodilatation, and arteriography. Clinical examination must include palpation of the peripheral pulses; in all cases these were absent distal to the site of thrombosis, despite the presence of a good collateral circulation as demonstrated by arteriography. When the true or indifferent limbs are heated, the affected limb shows either complete absence or considerable limitation of reflex vasodilatation, compared with a normal response in the corresponding unaffected extremity. This is stated to be the result of (i) reduction of the available channels by which the rest of the blood flow of the extremity might be augmented, and of vasoconstriction of collateral channels. The latter possibility is suggested because in 2 cases the amount of the vasodilatation obtained in the affected extremity by reflex measures was appreciably less than that subsequently obtained by preganglionic sympathectomy. Arteriography under spinal anaesthesia was performed on the cases in which the femoral artery was affected. It is of great value in determining the exact situation and extent of the thrombus and the state of the collateral circulation. Arteriograms demonstrate that in 2 cases there is a "filling defect" in the artery either beginning or ending abruptly. In the third case this clearly defined termination is not seen, but in this the arteriogram was made 2 years after preganglionic sympathectomy.

Pathological material was obtained in 2 cases (1 brachial and 1 femoral). The lumina of the affected vessels were found to be filled with well-organised and partly recanalised thrombus. The arterial walls showed damage chiefly to the intima, splitting of the internal elastic lamina, and slight focal damage in the media. The authors state that the damage to the elastica and media excluded thrombo-angiitis obliterans and that the causative process was probably trauma. In the case where the brachial artery was thrombosed, there was marked crenation of the intima of the digital arteries, suggesting long-standing vasospasm.

The condition is differentiated from other forms of arterial disease by the age and general good health of the patient and the fact that the abnormality is confined to one limb without any evidence of involvement of the vessels of the others. In the cases the Wassermann and Kahn reactions were negative.

Treatment consists of preganglionic sympathectomy and arteriectomy. One case remains relatively well 2 years after treatment by preganglionic sympathectomy alone. Arteriectomy may be called for under two sets of circumstances: (i) when there is evidence that the thrombosed segment of artery is reducing the available circulation by imposing spasm on collaterals, and (ii) when it appears likely that the thrombus may extend to block important and still patent collateral arteries. Preganglionic sympathectomy may be sufficient to deal with the former, the latter possibility can be determined only by arteriography, which may also demonstrate that arteriectomy would be difficult, if not impossible, without the sacrifice of a branch which is contributing substantially to the collateral circulation. Arteriectomy alone is insufficient; the patient so treated returned later having lost other fingers, and requiring preganglionic sympathectomy.

414

A PATHOLOGIST LOOKS AT ISCHÆMIA

by W. Blackwood, *Edinburgh Medical Journal*, 51, 131-144, March 1944

This is a short review of the common causes of ischaemia in the limbs, of the effects of this ischaemia and of the factors modifying these effects. Certain aspects are amplified by clinical descriptions, and appropriate histological material is illustrated by photographs. The causes of ischaemia are divided into those primarily due to (i) structural abnormalities, i.e. chronic arterial disease, thrombo-angiitis obliterans, traumatic arteritis, embolism and thrombosis; and those primarily due to (ii) functional abnormalities, i.e. the abnormal response of Raynaud's disease. The effects of ischaemia upon appearance and function are considered in relation to the pulse, skin temperature and colour, muscle power and nerve function; and the general structural changes and those in muscle and nerve are described.

Three cases are cited in which muscle biopsy was used to establish the diagnosis. One was a boy with a denervated ischaemic upper limb; the problem was whether the distal muscles were sufficiently alive for nerve suture to be worthwhile. The second was a case of persisting nerve and muscle

dysfunction following dislocation of the shoulder; the problem was whether this was due to nerve injury or to ischæmia. The third was a case of post-traumatic swelling of debatable origin in the thigh muscles, which was shown to be necrotic muscle. The second plate of illustrations is arranged so that the reader can readily distinguish the points of histological difference between denervated and severely ischæmic muscle.

The last section deals with the factors modifying the effects of ischæmia, i.e. the available blood supply, the metabolic demands of the tissues, the rate at which ischæmia develops and the duration of the ischæmia. The paper ends with a plea for the investigation of vascular problems by members of various departments working as a team.

415

VOLKMANN'S ISCHÆMIC CONTRACTURE

by D. L. Griffiths, *British Journal of Surgery*, 28, 239-260, October 1940.

This comprehensive and authoritative paper is the text of a Hunterian Lecture delivered to the Royal College of Surgeons of England. Volkmann first reported in 1872 the rapid post-traumatic muscle contracture which subsequently became identified with his name. The condition is extremely rare, and the author shows that it developed in only 8 of 21,000 fracture cases receiving primary treatment in clinics directed by Professor Harry Platt of Manchester.

In a series of 32 cases encountered by the present author, the antecedent lesions were of the elbow (15), forearm (12), wrist (1), whole upper limb (1). The remaining 3 cases followed embolism of the brachial (1) and common femoral (2) arteries. The author briefly reviews the clinical features of the condition, emphasising the importance of cyanosis and swelling of the fingers as an early, though not invariable, sign. In severe cases absence of the radial pulse is probably a constant sign in the first 3-4 days. The author's description of the macroscopic and microscopic appearances of the affected muscle is illustrated by photographs and is consistent with previous accounts. Diagnosis in typical and established cases is easy, but in some cases there may be difficulty in distinguishing the condition from certain nerve palsies or muscle contractures after infected wounds.

The author reviews the literature on the pathogenesis of the condition, and discusses external compression, nerve injury, venous obstruction, arterial injury and embolism, the mechanism of the ischæmia, and the experimental production of a similar condition in animals. In a series of experiments on a small number of rabbits, he was unable to produce the Volkmann syndrome by the prolonged application of tourniquets to the hind limb (with or without ligature of the common femoral artery) or by ligature of the femoral artery with or without the vein (but without any tourniquet), or by any combination of ligatures applied to any or all of the external iliac, the common femoral, superficial femoral, and popliteal arteries. If, however, the common femoral and common iliac arteries on the same side were tied simultaneously, thus obstructing both main vessels and collaterals, a Volkmann type of contracture followed in 5 out of 10 rabbits. The remaining 5 failed to survive this operation.

On the basis of the clinical and experimental observations reported, the author concludes that Volkmann's ischæmic contracture is due to arterial injury and to the accompanying spasm of the arterial circulation. He stresses the importance of early preventive treatment, which must take the form of operative relief of arterial obstruction. Treatment of established contracture is also briefly discussed. On the whole, the prognosis is poor.

REFERENCE

Volkmann, R. von (1872) *Handbuch der Chirurgie* (Pitha-Billroth), 2, 846

416

TRAUMATIC ISCHÆMIA IN THE FOREARM AND LEG

by S. Stanford, *Lancet*, 1, 462-463, 8/4/44

The author reports 2 cases of ischæmia following fractures. The first, a boy of 8, was admitted with a supracondylar fracture of the humerus. After an immediate reduction of the fracture, radiography showed redisplacement, and reduction was again undertaken with direct x-ray control. Some hours later, there was a median nerve palsy and absence of the radial pulse. The antecubital fossa was explored and the brachial artery was found to be white, contracted, and non-pulsatile. Blood-clots and several small fragments of bone were angulating and compressing the artery from behind. These were removed, without immediate improvement. Procaine (1%) was injected into the adventitia of the brachial, radial, and ulnar arteries and periarterial stripping of the lower 3 inches [about 7.6 cm.] of the brachial artery was performed.

This was followed by immediate improvement, and there was ultimate good recovery, although biopsy of the forearm flexors 1 year later showed some muscular atrophy. The author suggests that the circulatory improvement at operation was "due just as much to the mechanical release of the bony obstruction as to release of the arteriospasm by stripping."*

The second case was of a man with a severe comminuted fracture of the tibia and fibula. After manipulation and application of a plaster case, there was evidence of defective circulation and the plaster was split. Some months later there was considerable muscular atrophy and impairment of circulation. There were gross trophic changes of the toes. The dorsalis pedis artery was just palpable, but no pulsation could be felt in the posterior tibial artery. Biopsy of calf muscle 18 months after the accident showed evidence of severe atrophy of muscle. Blood vessels and nerves appeared normal. The author refers to 6 cases of anæsthesia and muscle degeneration described by Parkes (1943), who suggested that tight plasters had interfered with the vascular supply of the nerve trunks and described the condition as "traumatic ischæmia of the nerve trunks." The present author suggests that his second case was also of this type, and regards the histological finding of muscle atrophy but no infarction as confirming this view.

REFERENCE

Parkes, A. (1943) *Lancet*, 2, 15

417

VOLKMANN'S ISCHÆMIA OF THE LEG

by M. Albert & W. R. D. Mitchell, *Lancet*, 1, 519-522, 24/4/43

The authors describe 3 cases of injury to the lower extremity which they believe to have been followed by ischæmia of the Volkmann type of the muscles of the anterior tibial compartment. In 2 cases the injury had occurred in the war of 1914-1918, and there was in 1941 massive calcification in this region, as demonstrated radiologically and by surgical exploration. In the 3rd case, the injury was more recent (1941), and three months after the accident the anterior tibial compartment was occupied by a hard, painless swelling. This was found at operation to consist of dense fibrous tissue containing small blood vessels.

The authors give reasons for regarding the changes seen as due to a vascular injury, and not to direct injury of the affected muscles. They discuss in detail the theories which have been advanced by other writers in explanation of post-traumatic degeneration and subsequent calcification of muscle. They regard Volkmann's ischæmia as due either to temporary arterial obstruction or to venous occlusion. It is suggested that evidence of calcification may be available in old cases of this condition in the upper limb.

* [compare BMB 394]

BOOKS, MEMORANDA, REPORTS

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418/54

AIDS TO TROPICAL NURSING

by D. E. Cocker. London, Baillière, Tindall & Cox, 1944. 159 pages; 12 illustrations. 4s. [£0.2]

This is one of several concise textbooks which have been designed to cover the field of knowledge required of the modern nurse. Nursing is the one branch of the medical services in the tropics which requires development more than any other. It is essential that the training of such nurses should be undertaken by those who have had actual experience of tropical nursing. This book has been written by the Sister Tutor of the Presidency General Hospital, Calcutta, and includes much more information on tropical diseases than is found in the average medical nursing books. It contains the following chapters: (i) keeping fit in the tropics—personal hygiene, inoculations, food and drink; (ii) climatic disorders—glare, heat exhaustion, heat stroke, sun stroke, prickly heat; (iii) deficiency diseases of the tropics—beriberi, pellagra; (iv) nursing of tropical diseases; (v) summary of communicable tropical diseases; (vi) glossary. Chapter IV, treating of individual diseases, comprises the bulk of the book. There is an adequate index.

The information contained in this book is sufficient to fulfil the requirements of the examination syllabus of the General Nursing Council as far as tropical nursing is concerned.

The other books in this series deal with practical nursing, anatomy and physiology for nurses, hygiene for nurses, medicine for nurses, surgical nursing, gynaecological nursing, materia medica for nurses, fever nursing, tray and trolley setting.

418/57

NUTRITION AND NATIONAL HEALTH

by Sir Robert McCarrison. London, Faber and Faber, Ltd., 1944. 75 pages; 7 illustrations. 6s. [£0.3]

In 1936 Sir Robert McCarrison, formerly Director of Research on Nutrition in India, delivered three Cantor Lectures before the Royal Society of Arts. These lectures, which were published in pamphlet form, aroused considerable interest. They have for long been out of print and their re-publication in book form at a time when world-wide attention is being directed to the important part played by food and nutrition in health, is especially to be commended.

The three lectures expound the author's argument that properly constituted food is the greatest single factor in the promotion of good health and faulty food the greatest single factor in the production of bad health. McCarrison has performed experimental work of fundamental importance in the field of nutrition. He has produced peptic ulcer, urinary calculi, and many avitaminoses by faulty feeding of animals. Much of this work has been carried out in India, where the profound effect of food on physical efficiency is strikingly exemplified. These lectures provide experimental proof of the fundamental importance of food in relation to health. They are entitled: (i) food, nutrition, and health; (ii) relation of certain food essentials to structure and functions of the body; (iii) national health and nutrition.

418/58

TEXTBOOK OF SURGICAL TREATMENT

including Operative Surgery

edited by C. F. W. Illingworth. Second edition. Edinburgh, E. & S. Livingstone, Ltd., 1944. 564 pages; 230 illustrations. £1 10s. [£1.5]

Nineteen specialists have co-operated in the production of this textbook, under the editorship of the Regius Professor of Surgery in the University of Glasgow, and the book reflects the considerable personal experience of these contributors. As the editor points out, surgical treatment implies not only the actual surgical operation, but also many ancillary measures of preparation and after-treatment. It is devoted primarily to full accounts of pre- and post-operative measures; major operations and highly specialised procedures are dealt with in more general terms. In its first (1943) edition, the book was well received. This second edition has been revised to incorporate the most recent developments in surgical treatment; the chapter on burns has been rewritten, and some new illustrations have been included. The book attains a high standard of production, is well illustrated and adequately indexed.

Chapter headings: (i) pre-operative and post-operative care; (ii) wounds and wound infections; (iii) the treatment of burns; (iv) amputations; (v) affections of blood vessels; (vi) affections of the skull and brain; (vii) affections of the spine and spinal cord; (viii) peripheral nerve injuries; (ix) surgery of the autonomic nervous system; (x) diseases of bones; (xi) diseases of joints; (xii) tuberculosis of bones and joints; (xiii) paralysis and contracture; (xiv) fractures; (xv) affections of the shoulder region and arm; (xvi) affections of the elbow; (xvii) affections of the hand; (xviii) affections of the hip; (xix) affections of the knee; (xx) affections of the foot; (xxi) radiotherapy; (xxii) plastic surgery; (xxiii) affections of the face, mouth, jaws and salivary glands; (xxiv) affections of the neck; (xxv) affections of the thyroid gland; (xxvi) affections of the larynx, pharynx and oesophagus; (xxvii) affections of the breast; (xxviii) affections of the thorax; (xxix) hernia; (xxx) affections of the stomach and duodenum; (xxxi) affections of the intestines; (xxxii) affections of the rectum and anus; (xxxiii) affections of biliary tract, pancreas, and spleen; (xxxiv) affections of the appendix; (xxxv) affections of the kidney and ureter; (xxxvi) affections of the bladder and urethra; (xxxvii) affections of the male genital tract.

418/59

FORWARD SURGERY IN MODERN WAR

by W. H. Ogilvie. London, Butterworth & Co., 1944. 96 pages; 12 illustrations. 10s. 6d. [£0.525]

This gives a concise account of the primary treatment of battle casualties and is based on three years' surgical experience in Africa and the Middle East, where the author, a distinguished surgeon, served as consultant to the East Africa Force and afterwards to the Middle East Force. The book is intended for the general surgeon in one of the services who is already trained in operative technique but new to the surgery of wounds encountered in modern warfare. The chapters are entitled: (i) general principles of forward surgery; (ii) wounds; (iii) resuscitation; (iv) the surgical treatment of wounds; (v) x-rays: immobilization: evacuation; (vi)

418/55

GAS AND AIR ANALGESIA

by R. J. Minnitt. Second edition. London, Baillière, Tindall & Cox, 1944. 74 pages; 18 illustrations. 5s. [£0.25]

Nitrous-oxide-air analgesia is a comparatively modern method the relief of pain, and this little book gives a concise account of technique of administration, with particular reference to the anesthetic apparatus. It is addressed principally to the midwife who, under the supervision of the doctor, be required to use this method. The book is designed to diminish as far as possible the fortunes so often consequent upon faulty technique. The specialist anaesthetist will also find it a useful basis for lectures to midwives, while the general practitioner will see in it a simple explanation of the part he expects the midwife to take in the administration of analgesia in obstetrics. Chapter headings: (i) history of the method; (ii) apparatus and assembly; (iii) technique of administration in midwifery; (iv) contra-indications and causes of failure; (v) statistics and legislative developments; (vi) application to minor surgery. Appendixes: (i) self-administered analgesia for the midwifery of general practice; (ii) research notes.

418/56

ANTENATAL AND POSTNATAL CARE

by F. J. Browne. Fifth edition. London, J. & A. Churchill, Ltd., 1944. 622 pages; 87 illustrations. £1 4s. [£1.2]

Professor Browne is a leading advocate in Britain of the importance of improved antenatal care as a prime factor in the reduction of maternal mortality and foetal and neonatal morbidity. His book has grown much in size and reputation since it first appeared in 1935, and it is now the standard British work on the subject. The new edition includes an account of the Rh factor and erythroblastosis foetalis, and of recent work on diet in pregnancy, especially in preventing various diseases and accidents of pregnancy.

Chapter headings: (i) history and development of antenatal care; (ii) diagnosis of early pregnancy; (iii) examination of the patient; (iv) hygiene of pregnancy; (v) influence of the emotions upon pregnancy and parturition; (vi) constructive, educational and social aspects of antenatal care; (vii) heredity; (viii) maturity and post-maturity; (ix) abnormal presentations and positions; (x) multiple pregnancy; (xi) abnormalities in the quantity of amniotic fluid; (xii-xiv) hæmorrhage in early pregnancy; (xv) unsuccessful pregnancy; (xvi) the Rh factor and erythroblastosis; (xvii-xviii) hæmorrhage in late pregnancy; (xix) contracted pelvis and disproportion; (xx) displacements of the uterus in pregnancy; (xxi) vomiting in pregnancy; (xxii) the toxæmias of late pregnancy; (xxiii) diseases and disorders of the digestive system in pregnancy; (xxiv) diseases of the circulatory system in pregnancy; (xxv) diseases of the circulatory system; (xxvi-xxviii) diseases of the nervous system in pregnancy; (xxix-xxx) diseases of the ductless glands in pregnancy; (xxxi) diseases of the respiratory system in pregnancy; (xxxii) diseases of the urinary tract in pregnancy; (xxxiii) affections of the skin in pregnancy; (xxxiv) tumours complicating pregnancy, labour and the puerperium; (xxxv) venereal diseases in pregnancy; (xxxvi) the uses and value of radiology in obstetrics; (xxxvii) postnatal care.

wounds involving bones and joints; (vii) arterial injuries; amputations; (viii) abdominal wounds; (ix) chest wounds; (x) wounds of the head and face; (xi) burns; (xii) an outline of treatment at the base. The book is well arranged typographically; the illustrations consist of clear line drawings. There is no index, which is perhaps not a serious omission in a book of this size.

418/60

SURGERY OF MODERN WARFARE

edited by Hamilton Bailey. Sub-editor for medicine, C. Allan Birch. Third edition. Edinburgh, E. & S. Livingstone, Ltd., 1944. Part VI: 212 pages; 146 illustrations. 15s. [£0.75]

With this part, the third edition of *Surgery of Modern Warfare* is completed. Parts IV-V were reviewed in BMB 387/46. In Part VI are discussed (i) wounds of the large intestine; (ii) wounds of the rectum and buttocks; (iii) post-operative abdominal complications; (iv) wounds and injuries of the kidneys; (v) wounds of the bladder; (vi) wounds of the urethra; (vii) wounds of the scrotum, testicles and penis; (viii) heat exhaustion and other effects of heat; (ix) subtropical surgery; (x) the stretcher case; (xi) wounds in naval action; (xii) an outline of the medical services of the British army; (xiii) the transportation of wounded; (xiv) hospital organization in the Emergency Medical Service; (xv) the organization of a first-aid post. In an appendix of 30 pages Hamilton Bailey supplies some details omitted by the other contributors and reviews the literature which has appeared during the preparation of the book. Finally, a detailed index completes this work, which must be regarded as an outstanding contribution to the literature on war surgery.

418/61

BACTERIOLOGY FOR MEDICAL STUDENTS

by A. D. Gardner. Third edition. Oxford University Press; London, Humphrey Milford, 1944. 264 pages; 31 illustrations. 8s. 6d. [£0.425]

Bacteriology is a vast subject, and it is proper that the beginner should not too soon be overwhelmed with facts. This is a short readable account of the subject, confined to the needs of the student and general practitioner and omitting details of technique. It is thus well suited to serve as an introductory manual. The new edition includes an account of the most recent advances in immunology, disinfection, and chemotherapy, while the rest of the book has been carefully revised and the section on ultramicroscopic pathogens augmented.

Chapter headings: (i) microbes and their significance to man; (ii) form and structure of bacteria; (iii) cultivation of bacteria; (iv) pathogenic action; (v) the pyogenic cocci: *Staphylococcus*; *Streptococcus*; *Neisseria*; (vi) *Bacterium* (intestinal infections, etc.); (vii) *Bacterium*, *Proteus*; *Pseudomonas*; *Vibrio* (cholera); (viii) *Pasteurella* (plague); *Brucella* (Mediterranean and undulant fever); *Haemophilus* (whooping-cough, etc.); (ix) *Corynebacterium* (diphtheria); (x) *Mycobacterium* (tuberculosis, leprosy); *Actinomyces* (actinomycosis); (xi) spore-bearing rods, *Bacillus* (anthrax); *Clostridium* (tetanus, gas-gangrene, botulism); (xii) spirochaetes: *Treponema* (syphilis, etc.); *Leptospira* (infectious); (xiii) Protozoa (tropical diseases); fungi (skin infections); bacteria of minor importance; (xiv) ultramicroscopic agents: viruses; bacteriophage and border-line organisms; (xv) the defences of the body: immunity; hypersensitiveness; anaphylaxis; (xvi) the prevention of infection: sterilization; disinfection; antiseptics; chemotherapy.

418/62

PRACTICAL ANÆSTHETICS

for Students, Hospital Residents and Practitioners

by J. Ross Mackenzie. London, Baillière, Tindall & Cox, 1944. 63 pages; 136 illustrations. 10s. 6d. [£0.525]

The object of this manual is best stated in the words of the author, who intends it "to form a foundation on which the medical student and the medical or surgical hospital resident may build the practice of anaesthesia and analgesia and as a guide to the practitioner or the occasional anaesthetist, who desires to know the type of anaesthesia best suited to his patient in various circumstances." The practical aspect of the subject predominates in the descriptions of the anaesthetic agents and the methods of their administration. The recognition of anaesthesia as a speciality and the institution of a diploma in anaesthetics have in recent years raised the standard and status of anaesthetic practice in Britain. Chapter headings are: (i) preparation of the patient; (ii) pre-medication and basal narcosis; (iii) inhalation anaesthesia; (iv-v) the inhalation anaesthetic agents; (vi) the Nuffield Oxford ether vaporiser No. 1, rectal oil-ether anaesthesia, ethyl chloride anaesthesia; (vii-viii) the gas anaesthetic agents; (ix) endotracheal anaesthesia, trichloroethylene; (x) intravenous anaesthesia; (xi) local and regional analgesia; (xii) analgesia and anaesthesia in obstetrics; (xiii-xiv) complications and sequelæ of anaesthesia; (xv-xvii) the choice of the anaesthetic agent; (xviii) essential anaesthetic equipment with descriptive notes; (xviii) anaesthesia in infants and children; (xix) oxygen therapy and helium therapy; (xx) anaesthetics—to-day and to-morrow.

418/63

SOCIAL SERVICE IN A GENERAL HOSPITAL

by D. Manchée. London, Baillière, Tindall & Cox, 1944. 164 pages. 6s. [£0.3]

It is almost 50 years since the first hospital almoner in Britain started work at the *Royal Free Hospital*, London, her task being to ascertain the individual circumstances of each patient and to assist those whose home or financial circumstances were likely to prevent the patient from benefiting by hospital treatment. From this has sprung the hospital almoner of the present day, the "dispenser of the hospital's charitable services," whose medico-social work, carried out in close co-operation with the medical and nursing staff of the hospital, includes the collection of information regarding the patient's home and industrial life, help in alleviating factors likely to retard his progress to renewed health and a normal life; the provision of surgical and other appliances; the arrangement of convalescent and other institutional treatment; and district nursing, health visitors, and other aspects of after-care. Too often patients are ignorant of the services at their disposal. The hospital almoner thus has an important part to play in the field of social medicine.

Miss Manchée, who is Almoner at *St. Mary's Hospital*, London, and who therefore writes with practical knowledge of her subject, describes in detail the hospital social services in Britain at the present time. She has come to know the problems of the patient, both in peace and war, and her book is interspersed with many anecdotes, both sad and gay, which illustrate the varied nature of the work of the almoner. This book is important as being the first full account of medico-social work in the hospital; its publication coincides with the desire of many to learn more of this aspect of treatment and with the promise of a great post-war expansion of social medicine.

Chapter headings: (i) the purpose of hospital social service; (ii) the growth of industrialism; (iii) diagnosis and treatment of social distress; (iv) the expectant mother; (v) the sick child; (vi) care of the cancer patient; (vii) the diabetic; (viii) the ophthalmic department; (ix) the medical patient; (x) the orthopaedic; (xi) the almoner in casualty; (xii) needs of the air-raid casualty; (xiii) the clinic for venereal diseases; (xiv) convalescence; (xv) meeting the cost; (xvi) interviewing; (xvii) the almoner student; (xviii) functions of the almoner's department; (xix) equipment of the almoner's department.

418/64

THE BLOOD PRESSURE AND ITS DISORDERS INCLUDING ANGINA PECTORIS

by J. Plesch. London, Baillière, Tindall & Cox, 1944. 149 pages; 57 illustrations. 15s. [£0.75]

In this book, which Dr. Plesch describes as a companion volume to his larger work, *The physiology and pathology of the heart and bloodvessels*, an attempt is made to apply in practice the results of the experimental and theoretical investigations which the author has made of the blood pressure by means of the tonoscillograph. The tonoscillograph, of which the author is such a keen advocate, permits of the recording, as well as of the determination, of the arterial blood pressure, and has therefore the advantage over other methods of recording the blood pressure of providing a permanent record which can always be available for comparison with subsequent records. In addition it is claimed that it provides information concerning the state of the arterial wall. After demonstrating, with copious diagrams and equations, what is meant by the effective pressure, the maximum pressure, the minimum pressure, and the pressure amplitude, the book proceeds to deal with the clinical application of these observations, paying particular attention to angina pectoris, which is considered to be "a disease of the whole circulation," there being "no known fact which would justify the assumption that angina pectoris is specifically a heart disease." In addition to supplying a full exposition of the author's views on this question, treatment is detailed at considerable length. The book also includes sections on venous pressure and oedema.

418/65

THE DIAGNOSIS AND TREATMENT OF DELINQUENCY

Clinical Report on the Work of the Institute for the Scientific Treatment of Delinquency during the five years 1937 to 1941

by E. Glover. Published by the Institute, 17 Manchester Square, London, W. 1. 32 pages.

The Institute for the Scientific Treatment of Delinquency was founded in 1932, having for its object the provision of facilities for examination and treatment of anti-social conduct, particularly among young people. At first, physical examinations took place in premises lent by the *West End Hospital for Nervous Diseases*, but in 1937 the Institute opened a clinic with adequate equipment for examination, diagnosis and treatment of out-patient delinquents. In addition, the Institute has been active in the education of public opinion, the provision of training facilities for students and the organisation of centres outside London. It has not confined itself exclusively to the psychological or sociological interpretation of delinquency, but has developed a plan of research to cover the diagnostic and therapeutic fields.

This Report shows that 719 cases were referred to the Institute between 1937 and 1941. This clinical material is analysed as to sources, diagnosis, recommendations, disposal, psychological treatment, results, and after-history, and the Report concludes with a note on possible future developments in the diagnosis and treatment of delinquency.

GUIDE TO THE JOURNALS

Brain

67 : March 1944

- Pyramidal section in the cat. (E. G. T. Liddell & C. G. Phillips) 1-9
The nature of transient outbursts in the electro-encephalogram of epileptics. (D. Williams) 10-37
A form of familial presenile dementia with spastic paralysis. (C. Worster-Drought, J. G. Greenfield & W. H. McMenemey) 38-43
Meralgia parasthetica due to nodular lipomatosis and to traumatic lesions in the thigh: a reflex theory of sensory neuritis. (M. Kelly) 44-53
Recovery of spatial orientation in the post-traumatic confusional state. (A. Paterson & O. L. Zangwill) 54-68

British Journal of Ophthalmology

28 : July 1944

- The lacrimation reflex. (J. R. Mutch) 317-336
Vitamin P in ophthalmology. (W. R. Mathewson) 336-346
Desiccation keratitis. (J. E. M. Ayoub) 347-355
The secretion-diffusion theory of intraocular fluid dynamics. (V. E. Kinsey & W. M. Grant) 355-361
The late results of removal of intraocular foreign bodies with the magnet. (P. D. Trevor-Roper) 361-365

British Journal of Radiology

17 : July 1944

- Diverticulitis and diverticulosis. (N. P. Henderson) 197-203
A consideration of dose distributions in the treatment of intrinsic carcinoma of the larynx by radium implantation. (J. Morton, L. H. Gray & G. J. Neary) 204-212
Tomography of the temporo-mandibular joint and ramus of the mandible. (C. W. C. Gough) 213-215
German radiotherapy in 1942-1943. (H. C. Simchowitz) 216-217
Observations on radiolucency as a significant physical property of the acrylic dental materials. (G. L. Roberts) 218-220
Review of Scandinavian literature on gastro-intestinal diseases, 1939-1943. (E. Samuel) 221-225

British Journal of Surgery

32 : July 1944

- The effect of ligation on infection of the patent ductus arteriosus. (O. S. Tubbs) 1-12
War surgery in the Royal Air Force. (S. Cade) 12-24
The treatment of burns and wounds with skin loss by the envelope method. (R. P. Osborne) 24-32
The diagnosis of the depth of skin destruction in burns and its bearing on treatment. (D. H. Patey & R. W. Scarff) 32-35
Recent advances in the treatment of carcinoma of the mouth and jaws. (T. H. Somervell) 35-43
Injuries of the urinary bladder. (J. C. Ross) 44-49
Intraperitoneal chemotherapy. (R. H. Gardiner) 49-65
Shock: a consideration of its nature and treatment. (J. E. Dunphy) 66-74
Cholesteatoma of the petrous bone. (J. Pennybacker) 75-78
Cerebral neuroblastoma. (T. A. Ogilvie) 78-83
sulphanilamide treatment of fresh wounds in complete plasters. (J. Ewing, J. C. Scott, F. H. Masina, J. Trueta & A. D. Gardner) 83-84
ture scar-carcinoma of the lung and the "upper sulcus tumour" of the coast. (I. James & W. Pagel) 85-90
anal virilism: report of a case with unusual features. (N. G. B. McLetchie) 99

British Medical Journal

2 : 8/7/44

- ical view of shock. (V. Z. Cope) 35-36
ghts on four years of war surgery—1939 to 1943. (P. H. Mitchiner) 37-40
neuro-psychiatry at a Royal Air Force centre: an analysis of 2,000 cases. (S. I. Ballard & H. G. Miller) 40-43
Spontaneous renal apoplexy with resuscitation after cardiac arrest. (S. L. Governale & A. G. Rink) 43
Gonorrhoea in North Africa and the central Mediterranean. (D. J. Campbell) 44
An industrial rehabilitation centre. (F. D. Howitt) 52-53
Preventive medicine: teaching and practice. (J. M. Mackintosh) 53-54

2 : 15/7/44

- Current progress in sterilization of air. (S. Mudd) 67-70
Intravenous barbiturates in the treatment of hysteria. (C. Lambert & W. L. Rees) 70-73
Two cases of gunshot wound resulting from unusually large missiles: recovery. (R. Charles) 73-75
A modification of the invagination method of intestinal anastomosis. (J. B. Hogarth) 75-76
Method of locating a mobile renal calculus at operation. (B. W. Goldstone) 77-78
Self-medication and patent medicines. (J. N. P. Davies) 87-89

2 : 22/7/44

- Some problems in riboflavin and allied deficiencies. (H. S. Stannus) 103-105
Two years of military psychiatry in the Middle East. (H. B. Craigie) 105-109
Diagnosis and treatment of lesions due to vesicants. (W. E. Chiesman) 109-112
Rupture in a supposed lower segment Caesarean section scar. (D. W. James) 112-113
Meigs's syndrome: hydrothorax and ascites in association with fibroma of the ovary. (A. C. Clay, R. N. Johnston & L. Samson) 113-114

Bulletin of War Medicine

4 : June 1944

- The causes and prevention of delayed union of fractures. (Memorandum prepared by the Sub-committee on the Healing of War Fractures, of the M.R.C. War Wounds Committee) 559-561
The avoidance of infection around transfexion pins. (Memorandum prepared by the Sub-committee on the Healing of War Fractures, of the M.R.C. War Wounds Committee) 561

Glasgow Medical Journal

141 : January 1944

- Problems of infection. (C. H. Browning) 1-22
Simple polypoid tumour of the bronchus: report of a case. (R. Campbell & N. G. B. McLetchie) 23-27

141 : February 1944

- On growing up. Some observations, scientific and otherwise, on the surgery of childhood. (M. White) 37-49
A method of treating mammary abscess. (A. Lyall) 50-53

141 : March 1944

- Some aspects of aviation medicine. (H. E. Whittingham) 75-95

141 : April 1944

- A national plan of treatment for the chronic rheumatic diseases. (L. S. P. Davidson) 107-118

141 : May 1944

- Surgical relief of pain. (G. B. Mair) 139-147

141 : June 1944

- The transfusion of cell concentrates. (A. L. Goodall) 161-171

Journal of Mental Science

40 : April 1944

- Psychogenic amnesia: The refusal to remember. (D. N. Parfitt & C. M. C. Gall) 511-531
Psychosurgery: an evaluation of two hundred cases over seven years. (W. Freeman & J. W. Watts) 532-537
A case of narcolepsy with oniric manifestations. (D. Furtado & F. E. Pulido Valente) 538-549
Shock-therapy in psychoses: a possible rational basis and its clinical applications, based on three years' experience of its use in military psychiatry. (G. T. Stockings) 550-553
Some problems arising from a study of mental patients over the age of sixty years. (F. Post) 554-565
Psychoneuroses in R.A.F. ground personnel. (D. N. Parfitt) 566-581
A paranoid reaction associated with oculogyric crises and parkinsonism. (W. H. Gillespie) 582-587
An unusual brain injury: with a note on lesions of the superior cerebellar peduncle. (J. C. S. Thomas) 588-591
Eye movements in elements in electrical shock procedure. (F. F. Kino) 592-594
Parotid gland secretion in affective mental disorders. (H. J. Eysenck & P.-M. Yap) 595-602
Vitamins B₁ and C in effort syndrome. (P. G. Croft, M. S. Jones & D. Richter) 603-606

Lancet

2 : 8/7/44

- Visual problems of aerial warfare: I. "Night": studies in the dark-adapted eye. (P. C. Livingston) 33-38
Abdominal wounds: a clinical review of 65 cases. (H. G. Estcourt, J. A. Ross, S. H. C. Clarke & R. W. Ross) 38-41
Toxin reaction to thiourea: report on three cases. (C. R. St. Johnston) 42-43
Delayed suture of soft tissue wounds. (A. I. S. Macpherson) 43-44
Penicillin and smallpox: report of four cases. (W. D. Jeans, J. S. Jeffrey & K. Gunders) 44-45

2 : 15/7/44

- Vital statistics of 1943. (P. Stocks) 65-67
Visual problems of aerial warfare. II. "Day": studies in photopic vision. (P. C. Livingston) 67-73
Proflavine powder in wounds. (R. W. Raven) 73-75
Phosphatase and the repair of fractures. (G. Blum) 75-78
Impetigo contagiosa treated with microcrystalline sulphathiazole. (J. W. Bigger & G. A. Hodgson) 78-80

2 : 22/7/44

- Naval experience in relation to a National Health Service. (S. Dudley) 97-101
Dissection lobectomy for bronchiectasis: review of 100 cases. (T. H. Sellors, V. C. Thompson & G. Qvist) 101-103
The influenza "A" outbreak of October-December 1943. (C. H. Andrewes & R. E. Glover) 104-105
Vocational aspects of neurosis in soldiers. (A. Lewis & K. Goodyear) 105-109
Finger exerciser for burned hands. (M. C. Oldfield & C. J. King) 109
Hydronephrosis as a cause of backache. (P. C. Mallam) 110-111
Successful suture of finger flexor tendon. (R. M. Jones) 111

British Medical Bulletin is published by the British Council. One volume will appear each year, and each volume will contain a maximum of 12 parts, issued at approximately monthly intervals. The object of the Bulletin is to provide a guide to medical work in Britain. Requests from overseas for further information on any of the investigations reported, or for general information, bibliographies, and particulars of medical books and journals published in Britain should be addressed to the British Council, Medical Department, 3 Hanover Street, London, W.1, England

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BRITISH MEDICAL BULLETIN

Vol. 2 (1944)

No. 8-9

BLOOD

SPECIAL CONTRIBUTIONS

HUMAN BLOOD GROUPS	
by Dr. G. L. Taylor & Dr. R. R. Race	160
OBSERVATIONS ON INHERITANCE OF BLOOD GROUPS	
by Dr. R. R. Race	165
NATURE AND OCCURRENCE OF BLOOD-GROUP SUBSTANCES	
by Dr. W. T. J. Morgan	165
RECENT WORK ON ANÆMIAS	
by Dr. C. J. C. Britton	168
CLINICAL HÆMOGLOBINOMETRY	
by Dr. H. Scarborough	170
CIRCULATORY DYNAMICS OF HÆMORRHAGE	
by Dr. E. P. Sharpey-Schafer	171

REVIEW OF SELECTED PAPERS

Blood Groups	
Erythroblastosis Fœtalis : Fifty Families	173
Erythroblastosis Fœtalis : Treatment with Rh-Negative Blood	174
Distribution of Rh Factor in South Wales	174
Erythroblastosis Fœtalis : Survival of Transfused Erythrocytes	174
Erythroblastosis Fœtalis : Findings in 23 Cases	175
Erythroblastosis Fœtalis with Rh-Positive Mother	175
Erythroblastosis Fœtalis : Incidence, Diagnosis, Prognosis	176
Erythroblastosis Fœtalis : Preponderance of Rh-Positive Homozygous Fathers	176
Erythroblastosis Fœtalis : Pathological Findings in 52 Cases	176
"Incomplete" Antibody in Human Serum	176
Symptomless Incompatible Transfusion	177
Inheritance and Linkage Relations of Acholuric Jaundice	177
Group-Specific Substances in Tissues and Body Fluids	177

Anæmias and their Treatment	
Nutritional Iron-Deficiency Anæmia : I. Infants and Children	178
Nutritional Iron-Deficiency Anæmia : II. From Birth to 55 years	178
Anæmia and Diet in Women and Children	178
Discussion on Nutritional Anæmia in Women and Children	179
Treatment of Anæmia in Children with Iron and Ascorbic Acid	180
New Proteolysed Liver Preparation in Pernicious Anæmia	180
Sensitivity to Liver Extract	181
Autolysed Yeast in Nutritional Macrocytic Anæmia	181
Review of Hæmolytic Anæmias	181
Symptomatic Hæmolytic Anæmia	181
Acute Hæmolytic Anæmia : Case and Discussion	182
Destruction of Transfused Erythrocytes in Anæmia	182
Regeneration of Hæmoglobin and Life of Erythrocytes	183
Further Observations on Hæmoglobin-Regeneration	183
Refractory Anæmia : Sternal Biopsy	183
Refractory Anæmia : Hypocellular Normoblastic Marrows	184
Refractory Anæmia : Hypercellular Normoblastic Marrows	184
Anæmias of Pregnancy : Report and Discussion	185
Megaloblastic Anæmia of Pregnancy	185
Anæmia and Infection	185
Erythroblastic Anæmia of Childhood	185
Erythrocyte Transfusions : Report and Discussion	186
Erythrocyte Transfusions : 100 Cases	186

Other Blood Changes	
Thrombocytopenic Purpura	186
Observations on Experimental Thrombocytosis	187
Hæmorrhagic Disease of the Newborn	187
Elliptocytosis and Hereditary Hæmorrhagic Telangiectasia	187
Tropical Eosinophilia	188
Blood Dyscrasia after Arsphenamines	188

Hæmoglobinometry	
Alkaline Hæmatin Method	189
Simple Photoelectric Hæmoglobinometer	189

[continued overleaf]

REVIEW OF SELECTED PAPERS—continued

Plasma and its Constituents

Plasma-Protein Values in Infants	189
Plasma Proteins and Erythrocyte Sedimentation Rate	189
Changes in Stored Plasma and Serum	189
Accuracy of Serum-Protein Estimations	190
Fibrinogen Deficiency in Hæmorrhagic Disease	190

Circulatory Dynamics

Fainting in Blood Donors	190
Venous Pressure during Bleeding and Transfusion	191
Report on Fainting in Blood Donors	191
Methods of Estimating Blood Volume	191
Evans-Blue Method of Blood-Volume Estimation	192
Elimination of a Source of Error in the Evans-Blue Method	192

BOOKS, MEMORANDA, REPORTS...	193
------------------------------	-----

GUIDE TO THE JOURNALS	196
-----------------------	-----

This number of the Bulletin is a review of some recent work on blood and its disorders. The authors of the first paper, Dr. G. L. Taylor and Dr. R. R. Race, were until 1939 working on the serological aspect of human inheritance with Professor R. A. Fisher at the Galton Laboratory, University College, London. Brief reference to this work was made in BMB 346. On the outbreak of war, in anticipation of heavy demands for test-sera from military and civilian transfusion services, the Galton Laboratory unit was taken over by the Medical Research Council to form a Blood Grouping Serum Unit. In this period Dr. Taylor and Dr. Race have both published a number of papers on blood-grouping and other serological subjects, most of which are reviewed in this number.

Dr. W. T. J. Morgan is a member of the staff of the Lister Institute of Preventive Medicine, and Reader in biochemistry in the University of London. He has been an Honorary Secretary of the Biochemical Society since 1940 and was, from 1929 until 1937, First Assistant and Biochemist to the Institute's department for the preparation and study of therapeutic sera. His published work during the last 10 years has included many papers on immunochemistry. His chief interest has been in problems associated with the isolation of bacterial and tissue antigens in homogenous condition and yet retaining in full their "native" character. Dr. Morgan recently succeeded in combining non-antigenic polysaccharides which possess serological properties of biological interest, such as bacterial haptens, plant gums and specific blood-group substances, with certain bacterial proteins, thus forming potent antigenic complexes which induce the formation of immune-body specific for the polysaccharide component of the artificial antigen. The isolation of artificial antigenic complexes under what are almost physiological conditions, opens up a new line of approach to the problem of the nature, formation and occurrence of antigens in micro-organisms and animal tissues.

Dr. C. J. C. Britton is a graduate of the University of Otago, New Zealand. He first came to England in 1932 for two years as a research Scholar to the Bland-Sutton Institute of Pathology, Middlesex Hospital, London. Then, following three years as Assistant Pathologist to Christchurch Hospital, New Zealand, he was appointed Assistant Pathologist in the Bland-Sutton Institute and is now Officer in Charge of the Emergency Public Health Laboratory, Sector 5 (one of the laboratories of the Emergency Public Health Laboratory Service, which was described in BMB 64). Most of his published papers deal with hæmatological subjects. He is also author with Dr. L. E. H. Whitby of "Disorders of the Blood" (4th edition, 1944), and contributes the section on blood disease in the "System of clinical medicine" (12th edition, 1944).

Dr. Harold Scarborough is Temporary Assistant Physician in the Edinburgh Royal Infirmary. Formerly the holder of a Beit Memorial Fellowship for Medical Research, Dr. Scarborough has published work on a variety of nutritional subjects. He has made a detailed study of many problems involving capillary resistance, particularly in relation to the bleeding diseases. Since the war, Dr. Scarborough has been Principal Medical Officer and Deputy Director of the South-East Scotland Blood Transfusion Service. An account of a series of his papers on the properties of stored blood has already been given in BMB 94.

Dr. E. P. Sharpey-Schafer is First Assistant in the Department of Medicine of the British Postgraduate Medical School, London. Before the war he was particularly interested in endocrinology, and had published a number of papers on this subject. Since the war his interest has been diverted to problems in connection with the dynamics of the circulation.

SPECIAL CONTRIBUTIONS

420

HUMAN BLOOD GROUPS

G. L. TAYLOR, M.D., Ph.D., F.R.C.P.
and
R. R. RACE, M.R.C.S., L.R.C.P.

Human erythrocytes contain many different antigens (agglutinogens), usually demonstrated by agglutination on addition of serum containing corresponding antibodies (agglutinins). Besides antigens common to man as a species, there are others, present in some people and not in others, which enable us to divide mankind into several different systems of blood groups. The number of detectable antigens will no doubt be increased.

For many years it had been known that the serum of one species agglutinates the cells of another species of animal (heteroagglutination) when Landsteiner (1900), by finding that the sera of some human beings agglutinates the cells of

others, showed there were differences in the blood of members of the same species. The agglutination of the cells of one member by the serum of another member of the same species is isoagglutination.

ABO Groups

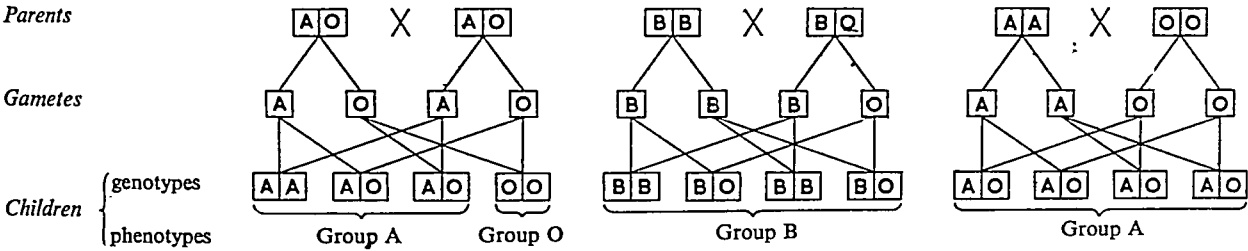
According to whether the cells contain one (A), the other (B), both (AB) or neither (O) of two antigens, A and B, Landsteiner and his colleagues classified mankind into four groups. Of all human erythrocyte antigens, A and B are the only ones for which the corresponding agglutinins occur naturally in human serum, and because antigen and corre-

sponding antibody may come together *in vivo*, the ABO groups are of great importance in blood transfusion. Landsteiner pointed out that a person's serum cannot contain the antibody (agglutinin) for an antigen (agglutinogen) present in his erythrocytes, but with very rare exceptions anti-A or anti-B agglutinins (or both) are found in the serum when the erythrocytes do not contain the corresponding antigen. The position is shown in the following Table :

TABLE I

Antigens in erythrocytes	O	A	B	AB
Antibodies in serum	Anti-A + Anti-B (alpha + beta)	Anti-B (beta)	Anti-A (alpha)	None
Janský classification	I	II	III	IV
Moss classification	IV	II	III	I

Instead of the alphabetical A, B, AB and O (O indicating absence of A and B) classification, based on the antigenic content of the cells, many workers, particularly in the past,



and leave only the specific anti-M or anti-N. Correct diagnosis of these groups requires very great experience.

Rh Factor

The latest factor, the Rh antigen (agglutinogen), was described by Landsteiner & Wiener (1940, 1941), who found that the serum of a rabbit or guinea-pig which had been injected with the erythrocytes of the Rhesus monkey agglutinated the cells of 85 % of white people in America and failed to agglutinate those of the other 15 %. The two classes are called Rh-positive and Rh-negative. The distribution is similar in Britain (Boorman, Dodd & Mollison, 1942; Hoare, 1943; Taylor & Race, 1944a), but there are marked racial differences. The proportion of positives is higher in American negroes, and Rh-negatives are very rare in some races; only one was found by Landsteiner, Wiener & Matson (1942) in 120 American Indians and one in 150 Chinese (Levine & Wong, 1943). Rh is inherited as a dominant character, the gene Rh determining its presence, and the gene rh its absence; its distribution is the same in the two sexes, and it seems to be quite independent of any other known blood-group antigen. It is present at birth.

Before long, agglutinins identical with anti-Rh were found in the sera of certain persons who had hæmolytic reactions following transfusion of blood which, according to the ABO groups, was compatible. The recipients were all Rh-negative and had either been transfused before, or were women receiving a transfusion in connection with childbirth. The first group had been immunized by earlier transfusions of positive blood; the second by Rh antigen present in the foetus and inherited from the father, the antigen having crossed the placenta from foetus to mother. When transfusion reactions due to anti-Rh were found in the mothers of infants suffering from hæmolytic disease of the newborn (erythroblastosis foetalis) the connection between immunization of the mother and this disease of the baby was quickly realized. According to Levine, Burnham, Katzin & Vogel (1941) it results from the isoimmunization of a mother by an erythrocyte antigen which she lacks, but which the child has inherited from the father, and the subsequent passage through the placenta of the resulting antibody to act on the susceptible foetal blood. As 90 % of the mothers concerned are Rh-negative, and anti-Rh can be found in the sera of a large proportion of them, and as every affected child of such a mother tested has always been Rh-positive, the importance of Rh in the causation of this disease cannot be doubted.

Confirmation of the part played by Rh in the aetiology of hæmolytic disease of the newborn has been provided by many workers, and in Britain by Boorman, Dodd & Mollison (1942, 1944); Taylor (1943); Race, Taylor, Cappell & McFarlane (1943); Hoaré (1943) and Langley & Stratton (1944). As soon as the importance of isoimmunization was understood, American workers began to treat affected infants by transfusion with Rh-negative blood, and Gimson (1943) has reported very encouraging results from a series so treated in London, whilst Mollison (1943) has followed the survival of the cells transfused into affected infants.

In the 10 % of cases where the mother is Rh-positive it seems that some other erythrocyte antigen must be responsible. Only anti-A and anti-B occur regularly in human sera under normal conditions; the sub-group antibodies alpha₁ and anti-O occasionally; and anti-M as a curiosity. Any of the above antigens, or some unknown and uncharted one, may possibly give rise to isoimmunization and cause a transfusion reaction or hæmolytic disease of the newborn. The recessive gene rh produces an antigen, and agglutinins which react with it have been made in mothers who lack it, by erythroblastotic babies who have got rh from their fathers, and it is

Essentials of the Rh Factor

When the erythrocytes of a Rhesus monkey are injected into the circulation of a rabbit (or guinea-pig), the serum of the rabbit may acquire the property of agglutinating the erythrocytes of some (about 85 %) human beings, but not of others (about 15 %).

Erythrocytes of the Rhesus monkey contain an antigen which causes the production of an antibody (anti-Rh agglutinin) in the serum of the rabbit.

The antigen in human erythrocytes which reacts with the anti-Rh agglutinin is called the Rh factor (Rh for Rhesus).

The Rh factor is present in the erythrocytes of approximately 85 % of human beings. Such persons are described as Rh-positive, and their erythrocytes are agglutinated by sera which contain anti-Rh agglutinin.

The remaining 15 % are described as Rh-negative—that is, their erythrocytes do not contain the Rh antigen, and are therefore not agglutinated by sera containing anti-Rh agglutinin.

When blood from an Rh-positive donor (that is, a donor whose erythrocytes contain Rh antigen) reaches the circulation of an Rh-negative recipient, the serum of the recipient may be stimulated to produce Rh antibody (anti-Rh agglutinin). That is, the Rh-negative recipient may react to the erythrocytes of the Rh-positive donor as the rabbit reacts to the erythrocytes of the Rhesus monkey.

If Rh antigen has previously reached the circulation of an Rh-negative recipient (by transfusion or via the placenta from the child of an Rh-positive father), anti-Rh agglutinin may be present in the serum, and subsequent transfusion of Rh-positive blood may result in hæmolytic reactions.

Anti-Rh agglutinin which has been produced in maternal serum passes across the placenta, reacts with the Rh antigen in the erythrocytes of the Rh-positive child, and causes hæmolytic disease of the newborn (erythroblastosis foetalis).

possible that quite a proportion of cases with Rh-positive mothers are caused by this type of agglutinin.

Rh Sub-types

The Rh factor is not as simple as was at first supposed. Wiener (1942) found a human serum which agglutinated only about 70 % of bloods (85 % were positive with the other human and immune animal sera). Rh-negative bloods did not react with the new serum and the 70 % which did were said, by analogy with the sub-groups of A, to be of the sub-type Rh₁, whilst the 15 % or so positive with the original and negative with the new serum, were of the sub-type Rh₂, as shown in Table IV.

Wiener (1942) referred to a peculiar agglutinin in the serum of an Rh₁ mother of an erythroblastotic infant. The serum, found by Levine, Javert and Katzin, was said to react with Rh-negative and Rh₂ bloods, that is, with about 30 % in all. Other accounts of this serum, named anti-Hr, because it worked, as it were, the other way round from anti-Rh, give different percentages of reactions and suggest that it was troublesome to work with. A similar, but not necessarily identical serum, called St from the first two letters of the mother's surname, has been investigated by Race & Taylor (1943), and details of its discovery and of the clinical

condition of the Rh-positive donor and her erythroblastotic baby have been given by McCall, Race & Taylor (1944). St reacts with the blood of all Rh-negative and all heterozygous Rh-positive persons (Rhrh), who are recognized by being Rh-positive parents or children of Rh-negative subjects, but it fails with about 20 % of bloods, all of which must be homozygous (RhRh) and represent about half of the Rh-positive homozygotes (about 38 % of the population).

TABLE IV

Erythrocytes	85 % human or animal serum	70 % serum (anti-Rh ₁)
Rh ₁ (70 %) . . .	+	+
Rh ₂ (15 %) . . .	+	—
Rh-negative (15 %) . .	—	—

To explain the sub-types Rh₁ and Rh₂, Wiener (1942) suggested that instead of the original genes Rh and rh, there were three allelomorphs Rh₁, Rh₂ and rh governing the heredity of the Rh factors. In a system of *n* allelomorphs the number of genotypes is given by $\frac{n(n+1)}{2}$. Thus Rh₁, Rh₂

and rh produce six genotypes, and if the frequencies of the genes are $\bar{R}h_1 + \bar{R}h_2 + \bar{r}h = 1.0$,* then the frequencies of the six genotypes are given by the terms of

$$(\bar{R}h_1 + \bar{R}h_2 + \bar{r}h)(\bar{R}h_1 + \bar{R}h_2 + \bar{r}h).$$

Race & Taylor (1943) suggested that the 20 % of cells which were St-negative were of the genotype Rh₁Rh₁. By taking the square roots of 0.20 and of 0.15, values of 0.45 and 0.39 are obtained for the frequencies of the genes Rh₁ and rh, leaving 0.16 for that of Rh₂. The percentages of the six genotypes calculated from these frequencies are given in Table V.

Striking confirmation of the belief that St-negative cells are Rh₁Rh₁ is provided by these genotype frequencies: (i) Those containing Rh₁ total 69.5 %, a figure in remarkable agreement with the 70 % of reactors with Wiener's anti-Rh₁ serum (the sub-type Rh₁). (ii) The genotypes Rh₂Rh₂ and

* [The bar over the gene indicates the frequency of the gene as opposed to the gene itself, e.g., the frequency of the gene Rh is written $\bar{R}h$.]

TABLE V

Phenotype	Genotype	% (approx.)	Frequency
Sub-type Rh ₁	Rh ₁ Rh ₁	20.0	$\overline{Rh_1}^2$
	Rh ₁ Rh ₂	14.4	$2\overline{Rh_1}\overline{Rh_2}$
	Rh ₁ rh	35.1	$2\overline{Rh_1}rh$
Sub-type Rh ₂	Rh ₂ Rh ₂	2.6	$\overline{Rh_2}^2$
	Rh ₂ rh	12.5	$2\overline{Rh_2}rh$
Rh-negative	rhrh	15.0	\overline{rh}^2

Rh₂rh total 15.1% and are the sub-type Rh₂ which Wiener had found to be 15%.

Shortly after the discovery of St serum, Race, Taylor, Boorman & Dodd (1943) found another type of anti-Rh serum from the mother of an erythroblastotic infant. This serum agglutinated about 30% of bloods, but failed to agglutinate Rh-negatives. The three genotypes in Table V which contain Rh₂ total 29.5%, and it was soon realized that the latest serum reacted with Rh₂. A similar anti-Rh₂ serum was described by Wiener (1943a). Within a week or two, Race, Taylor, Cappell & McFarlane (1944) identified a serum as anti-Rh₁, and it was then possible to test cells with the four different types of serum. The reactions caused by the three genes are:

TABLE VI

	Antisera			
	Anti-Rh	Anti-Rh ₁	Anti-Rh ₂	St
Rh ₁	+	+	—	—
Rh ₂	+	—	+	+
rh	—	—	—	+
and by the six genotypes:				
Rh ₁ Rh ₁	+	+	—	—
Rh ₁ Rh ₂	+	+	+	+
Rh ₁ rh	+	+	—	+
Rh ₂ Rh ₂	+	—	+	+
Rh ₂ rh	+	—	+	+
rhrh	—	—	—	+

Although it includes the most important part, the above description of the three antigens Rh₁, Rh₂, and rh and the reactions given by the four types of antiserum is not the whole story of the Rh antigens and antisera. Besides the three common allelomorphs Rh₁, Rh₂, and rh, four rare ones have been found, Rh', Rh'', Rh₀, each having a frequency of 1% or less, and Rh_y, which is very rare indeed (Wiener, 1943b; Race, Taylor, Cappell & McFarlane, 1944; Race & Taylor, 1944). With seven allelomorphs there are 28 genotypes. The six common ones in Table V are the genotypes of about 93% of people, and the remaining 22 genotypes cover the other 7%. Each Rh antiserum mentioned so far contains one agglutinin: (i) The 85% reacting serum of Table IV, anti-Rh, contains one agglutinin which by analogy with the use of the Greek alpha and beta for the anti-A and anti-B of the ABO groups may be called rho. (ii) Anti-Rh₁ contains rho₁, and (iii) anti-Rh₂ has rho₂. But sera containing mixtures do occur; thus anti-Rh' has rho + rho₁ and, anti-Rh'' has rho + rho₂. Details are given in the following Table:

TABLE VII

Antiserum	Percentage of people positive	Agglutinins	Reacts with Antigens Rh ₁ Rh' Rh ₂ Rh'' Rh ₀				
Anti-Rh	85	rho	+	—	+	—	+
Anti-Rh ₁	70	rho ₁	+	+	—	—	—
Anti-Rh ₂	30	rho ₂	—	—	+	+	—
Anti-Rh'	87	rho + rho ₁	+	+	+	—	—
Anti-Rh''	85 +	rho + rho ₂	+	—	+	+	+

St reacts with about 80% of people, including all rhrh; it also reacts with rh and Rh₂ wherever they occur, thus:

TABLE VIII

	Rh ₁	Rh'	Rh ₂	Rh''	Rh ₀	rh	Rh _y
St serum	—	—	+	+	+	+	—

Apart from its being negative with St and positive with rho₂, the reactions of Rh_y are not yet known.

Stratton (1944) has described a maternal serum which contains the three agglutinins rho, rho₁ and rho₂, and the authors of this article are aware of the occurrence of another serum of this sort.

The terminology used in the present account of the Rh system of blood groups will certainly not be permanent. Race (1944) has described a most ingenious and attractive scheme, formulated by R. A. Fisher, for the Rh genes, antigens and antibodies. The scheme postulates the existence of an eighth allelomorph, Rh₈, and two further agglutinins both different from St, but like St reacting with rh. The terminology of the scheme differs markedly from any used so far.

In seeking Rh-negative bloods for transfusion, those not agglutinated by 85% anti-Rh serum should be further examined with sera containing rho₁, and, if available, rho₂, otherwise the rare genotypes Rh'Rh', Rh'rh, Rh''Rh'', Rh''rh and Rh'Rh'' will be diagnosed as Rh-negative and may, on transfusion into a person with a corresponding agglutinin, cause a haemolytic reaction. About half the human sera are anti-Rh', so that the use of the rare Rh' type as negative blood is very risky. With Rh'' the risk is much less, as sera having rho₂ are very rare. By using an anti-Rh' serum for routine testing of donors almost all the risk would be eliminated. When persons of the five Rh' and Rh'' types are transfused it will usually be safest to give Rh-negative blood. The very infrequent Rh'Rh' may, however, make St antibody for which negative blood is incompatible. These possibilities emphasize the value of direct matching of the recipient's serum and intended donor cells in a tube at 37° C. These rare genotypes have increased the number of Rh-positives from 85 to 87% and have reduced the complete negatives to 13%.

In Table IX are set out the reactions given by the antigens and the various antisera, and in Table X are the phenotypic combinations, the interpretation in terms of genotypes, and the approximate frequencies.

TABLE IX

Antigens	Frequency (%)	Antisera					
		Rh	Rh ₁	Rh ₂	St	Rh'	Rh''
Rh ₁	0.43	+	+	—	—	+	+
Rh ₂	0.15	+	—	+	+	+	+
Rh ₀	0.01	+	—	—	+	—	—
	or less						
Rh'	"	—	+	—	—	+	—
Rh''	"	—	—	+	+	—	—
rh	0.36	—	—	—	+	—	—
Rh _y	very rare	?	?	+	—	?	+

The reactions with anti-Rh' and anti-Rh'' sera, included in the Tables for completeness, do not add anything to the information given by the other four sera. It will be seen that the majority of genotypes are not completely isolated, but that in most groups there is one very much more frequent than the rest.

Serological tests do not differentiate between Rh₂Rh₂ and Rh₂rh, but the genotypes of about 80% of people can be determined (Race, Taylor, Cappell & McFarlane, 1944), ignoring the rare ones, and some of these can be inferred from family investigations. In about three cases out of four, serological tests show whether an Rh-positive person is homozygous RhRh or heterozygous Rhrh, and are of great prognostic importance in families in which erythroblastosis foetalis has occurred (Taylor & Race, 1944b). Knowledge of the genotypes should increase the usefulness of the Rh group in linkage studies.

TABLE X

Antigens	Antisera						Frequency (approx.) (%)
	Rh	Rh ₁	Rh ₂	St	Rh'	Rh''	
Rh ₁ Rh ₁ }	+	+	—	—	+	+	19
Rh ₁ Rh'							Rare
Rh ₁ Rh ₂ }	+	+	+	+	+	+	13
Rh ₁ Rh''							Rare
Rh'Rh ₂ }							Rare
Rh ₂ Rh ₂ }							2
Rh ₂ rh							12
Rh ₂ Rh''	+	—	+	+	+	+	Rare
Rh ₂ Rh ₀ }							Rare
Rh ₀ Rh''							Very rare
Rh ₁ rh							33
Rh ₁ Rh ₀ }	+	+	—	+	+	+	Rare
Rh'Rh ₀ }							Very rare
Rh ₀ Rh ₀ }	+	—	—	+	+	+	Very rare
Rh ₀ rh							Rare
rh rh	—	—	—	+	—	—	13
Rh'rh	—	+	—	+	+	—	Rare
Rh''rh							Rare
Rh'Rh''	—	—	+	+	—	+	Very rare
Rh'Rh''	—	+	+	+	+	+	Very rare
Rh'Rh''	—	+	—	—	+	—	Very rare
Rh ₁ Rh _y	+	+	+	—	+	+	Very rare

Other Rh_y genotypes are very rare and have doubtful reactions.

Genetic and Forensic Implications

The importance of blood groups is not confined to their relationship to transfusion. As they provide markers for the chromosomes concerned with their inheritance, they are of interest to the geneticist. For the genes of another hereditary character may be on the same pair of chromosomes as those of a system of blood groups, and the transmission of the two may be related. ABO and MN tests are widely used in cases of disputed parentage and other medico-legal grouping tests are made on blood and stains. The six A₁A₂BO and the three MN groups furnish 18 blood-group types and with the 1 Rh divisions of Table X enable the recognition of 8 × 11 (198) different types. Other factors have been found, but because of technical difficulties or because the antibodies are not easily obtained, they are not yet widely used. Anti-P from normal or immune animal sera and occasionally from human sera (Landsteiner's extra agglutinin No. 1) differentiates P (a dominant character) and non-P persons.

The ABO antigens are not confined to erythrocytes, but occur in tissues and various body fluids. Many workers have thought that M, N and Rh antigens do not exist outside the erythrocytes, but Boorman & Dodd (1943) have confirmed

the report of Kosjakov & Tribulev (1940) that M and N do, and in addition have found Rh in tissues and saliva.

People can also be divided into two types according to whether the saliva contains in considerable amount the antigens of the ABO group to which they belong (secretors), or lacks them almost entirely (non-secretors). In secretors the antigens are in most other body fluids besides saliva. The ability to secrete A, B or O is a dominant character and its inheritance is quite independent of that of the groups themselves. It is not known whether the gene which controls secretion of ABO antigens governs the secretion of other antigens, e.g. Rh, or even whether the presence of Rh in saliva is an inherited character. The genes for the various blood groups and secretion appear to be on different chromosomes and so provide linkage markers for five (excluding sex) of the 24 pairs of chromosomes, whilst the characters themselves permit the division of mankind into a very large number of types thus:

TABLE XI

$$\text{ABO MN Rh P Secretion} = 792 \text{ types}$$

$$6 \times 3 \times 11 \times 2 \times 2$$

Ability to recognize more Rh genotypes or the discovery of other antigens would greatly increase the number of types, and Landsteiner suggested the possibility of establishing the individuality of blood just as can be done with finger-prints.

The proportion of people in the types varies enormously; some are very rare. There are great racial differences which are of interest to the anthropologist (see Table XII).

TABLE XII

	O	A	B	AB	
Britain %	46	42	9	3	But marked differences in different parts.
India %	30	24	37	8	Very great differences in different parts.
Most places %	M 30	MN 50	N 20		Occasionally a race has little of one or other antigen.
America % (whites)	P 75-80	Non-P 20-25		Secretor 75-80	Non-secretor 20-25

Rh has been mentioned above, and evidence of marked racial differences in the distribution of the Rh genes is being obtained.

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¹ [see BMB 438]

⁴ [see BMB 427]

⁷ [see BMB 431]

¹⁰ [see BMB 426]

² [see BMB 8]

⁵ [see BMB 428]

⁸ [see BMB 429]

¹¹ [see BMB 85]

³ [see BMB 432]

⁶ [see BMB 430]

⁹ [see BMB 435]

¹² [see BMB 433]

SOME RECENT OBSERVATIONS ON THE INHERITANCE OF BLOOD GROUPS

R. R. RACE, M.R.C.S., L.R.C.P.

The statistical methods and the appropriate family investigations necessary to show how blood-group antigens are inherited slowly emerged from the work on the ABO and MN systems. Consequently, when the Rh groups were discovered by Landsteiner and Wiener, this familiarity with the problem contributed to the fairly rapid recognition of seven allelomorph forms of the gene responsible.

The A_1A_2BO genes occupy a single locus, and so do the MN genes, and it was generally supposed that there was but one locus for the seven alternatives of the Rh gene. Early in this year, however, in order to correlate the three categories antigens, genes or allelomorphs, and antibodies, Fisher (Race, 1944) suggested that either each gene is associated with three antigens, or that three closely linked loci are involved. Each of Fisher's three antigens has two alternatives and these three pairs of two alternatives make eight possible combinations in the gamete. The hypothesis thus predicts the discovery of an eighth allelomorph.

Landsteiner & Wiener (1941), in the earliest family investigations, demonstrated that the Rh gene was not sex-linked nor partially sex-linked, and that it must therefore be carried on one of the 23 autosomes. Linkage was looked for, but not detected, between the Rh gene and the ABO and MN genes. So far no results have been published of any search for linkage between the Rh gene and a disease gene, nor between it and the remaining two common recognisable genes—those responsible for tasting phenyl-thiocarbamide and for secreting the ABO antigens in the saliva.

It has been known for some time that gypsies of Hindu origin, who have lived in Hungary for more than 200 years, have the modern Hindu distribution of the ABO groups; and that German colonists who settled in Hungary some 250 years ago, and did not intermarry with the Hungarians, have the modern German distribution. Both these distributions are quite unlike that of the Hungarians. Early in the present war the frequency of the ABO groups amongst donors in the United Kingdom was analysed by Fisher & Taylor (1940); the Scottish and North Irish frequencies were like those found in Iceland, but quite unlike the continental and South English distribution. This suggests that these northern frequencies may have been much the same since Viking times. Further, Hart (1944) finds that in the rural population of Ulster the donors with English names have the English distribution of groups although it is more than 400 years since their ancestors settled there.

Thus, when race-crossing is negligible, the proportions of the ABO groups probably remain constant over long periods of time. Consequently Ford (1942) considers these groups an example of a balanced polymorphism. This state entails, as shown by Fisher (1927), a balance of selective influences. In the case of these groups, selection may work on some unknown ancillary effect of the genes.

There is so far no clear evidence of the balanced nature of the polymorphism due to Rh. Indeed it has been argued by Haldane (1942) that the proportions of these groups in the white population must be changing fairly rapidly, owing to

the constant selection against the heterozygote, $Rhrh$, exerted by hæmolytic disease of the newborn. Such adverse selection would tend to bring to a very low level the rarer of the two genes — rh . The relatively high proportion of Rh-negatives amongst the whites is probably due, according to Haldane, to their having originated from a crossing of two races, one mostly Rh-positive (like the modern Chinese) and the other predominantly Rh-negative. Haldane therefore considers that the gene ratio amongst whites is highly unstable and that rh is in the process of being eliminated, the present polymorphism being of a transient type. Hogben (1943), on the other hand, thinks that the ratios are constant, and that the selection against the gene rh is counterbalanced by a high mutation rate to rh . The rate of mutation would have to be many times higher than any yet known.

Fisher has suggested another way in which the gene frequency of rh may be maintained in spite of hæmolytic disease. In human families deaths in infancy are usually associated with an increased number of births. In hæmolytic families, even with homozygous fathers, where every child is liable to the disease, not all are killed by it; in such cases additional births will have partially compensated for those lost. With heterozygous fathers, on the other hand, half the children will be recessives, like their mothers, and these will have the higher rate of survival, so that even a partial replacement of children lost may over-compensate the loss of rh genes.

There is then no solid ground for assuming that the rh gene is being eliminated, even if, as is still doubtful, Rh-negative women have on the average slightly fewer surviving children than Rh-positive women. The physiological and psychological tendencies to replace children lost early in life are illustrated in a series of families of hereditary acholuric jaundice collected by the writer (Race, 1942) when at the Galton Laboratory. It was then found that affected females had an exceptionally large number of stillbirths and infantile deaths, but, nevertheless, had a larger number of surviving children than their normal sisters.

In this case, still-births and neonatal deaths were a stimulus to over-compensation, and it is to be expected that mothers of children with hæmolytic disease, whose husbands are heterozygotes, $Rhrh$, may eventually produce more than their share of Rh-negative children.

Haldane (1942) has discussed the eugenic aspect of the Rh- rh gene substitution, and points out that, although it is responsible for more deaths than any other known human gene substitution, it is obviously going too far to recommend that Rh-negative women should marry exclusively Rh-negative men. The Rh-positive babies of only about 5% of Rh-negative women are affected with hæmolytic disease. Such women may possess highly permeable placenta, and if the abnormal permeability was due to a gene and the gene could be recognised, then there would be a strong case for discouraging a mating which involved (i) an Rh-negative woman and (ii) this gene for placental permeability and (iii) an Rh-positive man.

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¹ [see BMB 437]

² [see BMB 435]

OCCURRENCE AND NATURE OF HUMAN BLOOD-GROUP SUBSTANCES

W. T. J. MORGAN, Ph.D., D.Sc.

Rather more than 40 years have passed since Landsteiner and his pupils announced that human bloods can be divided into four serological groups. Although the modern technique of blood transfusion that has been evolved from this important

discovery is now to be regarded as an established and safe routine medical procedure, it is unfortunately not yet possible to record similar outstanding advances in what may be considered to be the fundamental aspect of the subject, namely,

the chemical nature of the substances that are directly responsible for the strict specificity of tissue cells and tissue fluids.

Many workers have at one time or another attempted to isolate the blood-group antigens from human erythrocytes but it may be said that, in general, these attempts have failed. The work has proceeded mainly along two lines: the extraction of the cells or stromata with simple aqueous reagents, or with organic solvents. In no instance has the isolation of any of the blood-group antigens from erythrocytes been recorded but, on the other hand, substances have often been isolated which, though devoid of antigenic power, have shown intense blood-group specificity.

Alcohol-Soluble Blood-Group Substances

The earliest observations dealing with this aspect of the subject were those of Schiff & Adelsberger (1924) and of Landsteiner & van der Scheer (1925), who obtained non-antigenic group-specific substances by extraction of erythrocytes with alcohol. Hallauer (1934), using a similar technique, described the isolation of specific non-antigenic substances from all three (A, B, O) blood groups. Apart from the conclusion based on a few qualitative tests that the specific substances are largely carbohydrate, the chemical nature of these immunologically active factors was not determined. The composition of the specific material isolated by Hallauer, which is very similar for each specific blood group examined, was 43–46% C, 7–8.5% H, 6.8–7.0% N, 15–21% P. The high P content, if present as P in organic combination, is of considerable interest but, so far, no further details have been given and no confirmation of these important observations has been forthcoming. More recently Stepanov, Kusin, Makajeva & Kosjakov (1940) have also described the isolation of specific group substances from erythrocytes by means of alcoholic extraction. Although these substances give strong *in vitro* reactions with the homologous immune-serum produced by means of the corresponding erythrocytes or stromata, the alcohol-soluble material is itself devoid of antigenic properties.

Water-Soluble Blood-Group Substances

The occurrence of the blood-group substances in a water-soluble form in the tissue fluids and secretions of the body has been known for many years and an examination of the extensive literature on the subject shows that an insight into the chemical nature of the specific A, B and O group substances has been attained almost entirely through studies on these water-soluble group components.

Blood Group A-substances from Peptone, Pepsin and Gastric Mucin from the Pig

An early observation of Schiff (1930) revealed that commercial peptone contains a substance which inhibits the hæmolysis of sheep erythrocytes by an immune-serum to human erythrocytes belonging to group A. The isolation and characterisation of the specific group A-substance from peptone was reported by Goebel (1938), who showed that the substance is largely composed of a polysaccharide which is rich in glucosamine. The purest specimens obtained, however, still showed a weak biuret reaction indicating the presence of protein or of some kind of amino-acid complex. The A-substance contained 45–46% C, 6–7% H, 5–6% N and 9–10% acetyl, and showed a weak dextro-rotation $[\alpha]_{5461} + 10^\circ$. An A-substance, probably identical with the A-substance obtained from peptone, has been isolated from commercial pepsin by Landsteiner & Harte (1940), and by Meyer, Smyth & Palmer (1937) as the result of their work on the glyco-proteins that are present in the gastric mucosa of the pig; these workers isolated from this tissue a polysaccharide which possesses intense A-activity and which contains *d*-galactose and N-acetylglucosamine in equimolecular quantities. Stacey (1943) has stated that the A-substance isolated from commercial pepsin contains *d*-mannose and *l*-fucose in addition to *d*-galactose and N-acetylglucosamine, but details of this work have not yet been published. The frequency with which the purified A-substance obtained from different sources was found to give a positive test for protein or for single amino-acids indicated that an amino-acid complex might be a true component of the specific A-substance. Landsteiner & Harte (1940) followed this clue by examining with more care the non-hexosamine nitrogenous constituents,

and found that the products of acid hydrolysis of the A-substance contained 35–40% of the total nitrogen in the form of amino-acids; arginine, histidine and possibly alanine were identified by simple colour reactions. The analytical figures found for the composition of the A-substance isolated from peptone, pepsin and gastric mucin of animal origin are almost identical. It seems probable that the A-substance in peptone is derived from the pepsin used in its preparation. Similarly the A-activity shown by commercial pepsin is most probably due to its content of A-substance derived from pig gastric mucin.

In most of the earlier work the activity of the A-substance isolated from different sources was determined by means of the hæmolytic inhibition test, with the result that the destruction of an important serological property of the native A-substance, the power to inhibit A-isoagglutination, was overlooked. Landsteiner & Harte (1940) observed that treatment of the crude A-substance with formamide at 150° C. for 1 hour according to a technique introduced by Fuller (1938) for the isolation of bacterial polysaccharides, gave rise to a purified A-substance which showed only a fraction of its original power to inhibit isoagglutination, whereas its capacity to inhibit the hæmolysis of sheep cells by an anti-A rabbit serum was actually increased beyond the original value. These and other observations indicated that a carefully controlled isolation procedure must be used if the blood-group complexes are to be obtained in their "native" condition, that is, with their chemical, physical and immunological properties unchanged. Fortunately, considerable experience with a closely related problem, the isolation of certain labile bacterial antigens (Morgan, 1937; Morgan & Partridge, 1939, 1940, 1941, 1942) became available a few years ago, and the application of this knowledge has enabled methods to be elaborated whereby the specific group A-substance can be isolated from commercial pepsin and crude gastric mucin and yet retain its original power to inhibit A-isoagglutination largely unimpaired (Morgan & King, 1943). The A-substance prepared by these methods is similar in composition to that described by Landsteiner & Harte (1940), but differs from it in a number of important physical and immunological properties. The material shows not only a high serological activity as determined by the inhibition of isoagglutination but also the high viscosity that is so characteristic of native gastric mucin. Furthermore a 1% solution of the A-substance possesses the property of forming an elastic gel on the addition of borate buffer at pH 8.5. This property is readily lost on heating the A-substance in neutral, acid or alkaline solution at 100° C. for a few minutes, and it has been found that the addition of the buffer to a 1% solution of the A-preparation reveals at once, according to the formation or otherwise of the elastic gel, whether the material has been degraded during the course of its preparation. In addition to the rapid decrease in the viscosity of the A-substance that is brought about by heating solutions of the substance, there occurs at the same time a steady fall in the ability of the preparation to inhibit the isoagglutination of the A-cells by natural human anti-A (α) agglutinin. In order to avoid these irreversible changes it is essential that only the most gentle methods of isolation should be employed.

The undegraded A-substance isolated by Morgan & King (1943) from crude pig gastric mucin shows two other important properties that are absent from material prepared by methods that involve heating the mucin or pepsin in formamide or in dilute sodium carbonate. One characteristic property retained by the undegraded A-substance, which is itself without antigenicity, is its power to combine with the protein component of the somatic O antigen of *Bact. shiga* to form an antigenic complex that gives rise to extremely potent and specific anti-A immune-body in the rabbit (Morgan 1941, 1943). The other property shown by the undegraded A-substance is its capacity to function as a bacterial "virulence enhancing" agent in the same manner as the crude gastric mucin of the pig. Both these properties are readily lost if the A-substance is heated or treated in any way that will destroy its viscosity or its capacity to inhibit A-isoagglutination, even when the power of the resulting material to inhibit the hæmolysis of sheep cells by anti-A serum is completely retained. The retention of these important properties of the native A-substance by carefully purified preparations completely justifies the extra trouble involved in the isolation of the blood-group substance.

The undegraded substance shows a high viscosity, η , 2.8

at a concentration of 0.5 % in saline. A typical analysis of the substance gave 45 % C, 6.5 % H, 6.0 % N and 10 % CH_3CO , and the material was found to be essentially homogeneous when examined at pH 4.0 or 8.0 in the Tiselius electrophoresis apparatus. Hydrolysis of the A-substance with 6N HCl gives rise to about 50 % reducing sugars, 27 % hexosamine, 4.5 % α -amino N (Van Slyke), and 2.2 % α -amino acid N. Treatment of the active material with 0.1 N sodium carbonate at 100° C. causes the complex to break up in such a manner that part of it will readily diffuse through a cellophane membrane while about two-thirds of the total material remains indiffusible. The amino-acid components are almost completely retained by the membrane and are still associated with a carbohydrate structure. The indiffusible complex, $[\alpha]_{5461} - 20^\circ$, is practically non-reducing, is electrophoretically homogeneous and possesses less than 1 % of the original serological activity. The diffusate, however, shows strongly reducing properties without further acid hydrolysis and gives an immediate colour with Ehrlich's reagent, thus indicating the presence of an oxazole structure which has most probably been formed by the action of the alkali on an N-acetyl hexosamine molecule that possesses a free reducing group at C atom 1 (Morgan & Elson, 1934; Morgan, 1936). The alkali-labile linkages in the original A-substance are presumably a part of those glycoside linkages that join the C atom 1 of the N-acetylhexosamine molecules to other components of the A-complex. The diffusible material contains a considerable amount of N that is not accounted for as hexosamine-N or α -amino acid N. The results so far obtained seem to indicate that some but not all of the N-acetylhexosamine molecules contained within the A-substance are joined at C atom 1 to the amino-acid components of the serologically active complex.

A preliminary qualitative examination of the amino-acids present in the products of acid hydrolysis of the A-substance has been made by means of the chromatographic method described by Consden, Gordon & Martin (1944). At least 15 amino-acids are present as components of the A-complex and it seems probable that threonine and hydroxyproline are present in higher concentrations than are normally found in proteins. Cystine appears to be absent. The isolation of threonine from A-substance has been described by Freudenberg, Walsh & Molter (1942).

Blood-Group Substances from Human Sources

The difficulty of obtaining sufficient group-specific substances from human erythrocytes for detailed immunochemical studies has forced workers in this field to consider human tissue fluids and secretions as a source of the specific group substances. The capacity of certain individuals to secrete in their tissue fluids substances that possess a serological specificity very similar to or identical with their specific blood-group substance is now generally recognised. Those individuals who secrete their blood-group substances in a water-soluble form in the tissue fluids are termed "secretors," whereas those who do not secrete the active factors are called "non-secretors." It has been established that the presence or absence of water-soluble specific blood-group substances in the secretions and tissue fluids of an individual is controlled by a single gene S, dominant in effect, which allows the secretion of the specific substance. There is no evidence of linkage between the character "secretor" and any of the A, B and O blood groups.

Urine: As a result of the detection of the specific blood-group substances in human urine by Yosida (1928), several early attempts were made to isolate the specific substances from this source, but apart from demonstrating that the active material is largely polysaccharide in nature and contains *d*-galactose and N-acetylglucosamine, little progress was made in determining the chemical nature of the group substances. Indeed, it was not possible to differentiate chemically between substances isolated from the urine of individuals belonging to groups A, B or O. A serious disadvantage in using urine as a source of the specific substance is its very small content of the serologically active factor, and work on urine as a starting material has now been largely abandoned.

Gastric juice: Witebsky & Klendshoj (1940) reported the isolation of the blood-group B substance from human gastric juice but again, apart from showing that the material isolated possessed strong B-specific serological activity and gave rise to 75 % of reducing sugars on acid hydrolysis, the results

gave little information concerning the chemical properties of this important substance. Material, 13.5 mg., containing about 1.5 % N was isolated from 110 ml. of gastric juice. Witebsky & Klendshoj (1941) have also described the isolation of a specific O-substance from human gastric juice. Owing to lack of material, detailed chemical examination of the specific substances was not possible.

Saliva: Specific blood-group substances have been obtained from human saliva by Landsteiner & Harte (1941) who recovered about 15 mg. of active substance from 500 ml. portions of the secretion. On a dry-weight basis, the substances were at least 50 times as active as the total solids in the saliva. The preparations made from the saliva from "secretors" belonging to groups A, B and O showed little difference chemically. The materials contained about 5.5 % N, 2.5 % α -amino-acid N, 21–23 % hexosamine and gave 45–48 % reducing sugar after acid hydrolysis. The Millon test for tyrosine, Ehrlich test for tryptophane with *p*-dimethylaminobenzaldehyde, and the lead test for sulphur were negative. Distinct reactions were obtained with diazotized sulphanilic acid and for arginine by means of Sakaguchi's test.

Pseudo-mucinous ovarian cyst fluids: The concentration of the active factors in saliva and gastric juice is high when compared with that of many other tissue fluids and secretions, but even here the active substance represents only a small part of the total solid matter of the secretions, which are, moreover, difficult to obtain in useful quantities. In certain instances, however, mucilaginous fluids accumulate in man as a result of pathological changes or of tissue overgrowth, and the knowledge that pseudo-mucinous ovarian cysts are of frequent occurrence prompted Morgan & van Heyningen (1944) to examine the fluid contents of these pathological overgrowths for blood-group substances. An examination of 50 pseudo-mucinous cysts revealed that, when these cyst fluids were obtained from women who possess the power to secrete their specific blood-group substance in a water-soluble form, the fluids are a convenient and potent source of the group-specific substances A, B and O. Cyst fluids vary in volume from 100 ml. to about 6 litres, and individual cysts from secretors belonging to group A have frequently been found to contain several grammes of the A-substance, which can be obtained pure by methods similar to those elaborated for the isolation of the A-substance from gastric mucin of the pig. The activity of the native cyst fluid was compared with that of known specimens of salivas on a dry weight basis by Morgan and van Heyningen, who showed that cyst fluids belonging to group A may contain up to one hundred times as much specific substance per ml. as is contained in the same quantity of a good specimen of A-saliva.

The A-substance present in the pseudo-mucinous ovarian cysts of secretors belonging to group A has been isolated by King & Morgan (1944) and its properties have been examined. The electrophoretically homogeneous substance contains 44–45 % C, 6.7 % H, 6.0 % N, 10 % CH_3CO and is weakly dextro-rotatory $[\alpha]_{5461} + 11^\circ$. Acid hydrolysis gives rise to about 50 % of reducing sugars, 25 % hexosamine, 4.4 % of α -amino N (Van Slyke) and 2.5 % α -amino-acid N. The A-substance behaves with dilute alkali exactly as had been described for the A-substance from gastric mucin of the pig.

The active cyst fluids from secretors belonging to groups B and O offer a convenient source for the isolation of the blood-group substances. Although this has not yet been satisfactorily accomplished, preliminary experiments have shown that there is a good chance of obtaining from cyst fluids B- and O-substances in useful quantities. The recently discovered Rhesus (Rh) factors do not appear to be present in significant quantities as water-soluble components of cyst fluids obtained from secretors or non-secretors belonging to the blood groups ARh, BRh and ORh. Similarly the M and N factors, as well as the Rh factors, appear to reside largely in the erythrocytes, and are not present in the tissue fluids and secretions in a water-soluble form (Kosjakov & Tribulev, 1940; Wiener & Forer, 1941; Levine & Katzin, 1941; Boorman & Dodd, 1943).

An Artificial Blood-Group A-Agglutinin

The results of investigations so far completed indicate that the substance present in commercial pepsin, peptone, hog gastric mucin, human saliva and pseudo-mucinous ovarian cyst fluid which possesses the serological characteristics of

the specific blood-group A-substance, is a polysaccharide-amino-acid complex. The undegraded substance is not antigenic by the ordinary tests, but possesses intense A-specific serological activity and is able to inhibit in extremely small amounts the agglutinating action of human anti-A (α) agglutinin on group A erythrocytes. The predominantly polysaccharide nature of the serologically active complex made it probable that it could be converted into an antigen showing A-specificity by means of a simple method originally used to convert certain non-antigenic specific bacterial polysaccharides and plant polysaccharides, such as agar, gum arabic and cherry gum, into antigenic complexes. These artificial antigens give rise in the rabbit to immune-body that is specific for the polysaccharide component of the antigenic complex (Morgan & Partridge, 1940, 1941; Partridge & Morgan, 1940, 1942).

The artificial complex can be made by simply mixing an aqueous solution of the A-substance with an alkaline solution of the conjugated protein component of the O somatic antigen of *Bact. shigae* or *Bact. typhosum*. The addition of acid to the mixed solutions to yield a final pH of about 4.5 gives rise to the water-soluble antigenic complex. Three intravenous doses, each of 0.05 or 0.5 mg., of the artificial complex will usually give rise to potent anti-A immune-body in those rabbits that already possess a natural but low titre anti-A agglutinin. A typical immune-serum of this type will agglutinate A₁ and A₁B cells at a dilution of 1:25,000 to

1:50,000 and A₂ and A₂B cells at 1:2,000 to 1:5,000, whereas B cells are agglutinated at a dilution of 1:25 to 1:100 and O cells at less than 1:10. In most instances the immune-body produced is largely common α in character. Potent immune anti-A sera engendered by the artificial complex have proved to be of value in the technique of differential agglutination, and, apart from their use as blood-grouping sera, are useful reagents for the detection of weakly reacting erythrocytes belonging to sub-groups of the A-agglutinin. In the light of these results there seems to be no reason why the water-soluble non-antigenic B- and O-specific substances present in human tissue fluids and secretions should not also be converted in B- and O-agglutinogens.

Increasing knowledge of the chemical and immunological properties of the specific group substances of erythrocytes, tissue cells, and fluids will provide a sounder basis for carrying out procedures such, for example, as the removal of unwanted isoagglutinins in human serum and plasma, the neutralisation *in vivo* by group-specific haptens of maternal isoagglutinins that give rise to foetal death, the selection of erythrocytes that will survive longest after transfusion, and the choice of suitable cells for tissue transplantation. The success of these procedures depends upon the correct application of an exact and detailed knowledge of specific chemical and immunological relationships. An almost inexhaustible field of biochemical investigation on group antigens and specific blood-group substances awaits exploration.

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423

RECENT WORK ON ANÆMIAS

C. J. C. BRITTON, M.D., D.P.H.

During the war steady extensions have been made in our knowledge of the anæmias. There has been, perhaps, only one dramatic advance and that is the elucidation of the aetiology of erythroblastosis foetalis.

Hypochromic Anæmias

Studies have recently been made in Britain by Davidson, Donaldson, Dyar, Lindsay & McSorley (1942, 1943, 1944), Wills, Mackay, Bingham & Dobbs (1942) and others on the wartime incidence of iron-deficiency anæmia. There appears to be a definite increase of anæmia, particularly in older children, and this has been related to the wartime diet. The importance of first-class proteins in the treatment of iron-deficiency anæmia has been rather neglected for some years except for the writings of Bethell (1936), but the work of Hahn & Whipple (1939) on dogs made anæmic by numerous bleedings at short intervals showed that, even in the presence of a large excess of iron, a low protein intake prevented the production of an adequate amount of globin and therefore of hæmoglobin. A case of severe microcytic hypochromic anæmia of long duration recently treated by the present writer gave a similar result. This patient showed only slight hæmoglobin production on intensive iron therapy, with or without vitamins and chlorophyll, but the institution of a

very high protein diet caused a reticulocyte crisis and led to rapid recovery.

Much work has also been carried out over the last 10 years on the mechanism of absorption of iron, but space does not permit reference to more than a few of the papers on this subject. Whipple and his colleagues at Rochester, N.Y., have gained interesting information by the administration of radioactive "tagged" iron. Most of the experiments have been carried out on dogs, but clinical experiments in man where possible have given similar results. Thus Hahn, Bale, Ross, Balfour & Whipple (1943) found that the normal non-anæmic animal absorbs little iron, but that chronic anæmia due to blood-loss increases the absorption of iron by 5-15 times. Acute anæmia by rapid blood-loss does not at once increase the rate of iron-absorption: the iron stores of the body are first depleted and only after several days does iron-absorption increase. Gastric, duodenal and jejunal experimental pouches all show active iron-absorption.

To the number of substances which can hinder the absorption of iron from the bowel, McCance, Edgecombe & Widdowson (1943) have recently added phytic acid, which is present in whole cereals, e.g. brown bread. This substance causes the formation of insoluble iron phytate which passes through the bowel unchanged.

Pernicious Anæmia

The work of Fox & Castle (1942) on ætiology is a real advance and helps to correlate the pathological findings in the stomach in pernicious anæmia with the site of production of the intrinsic factor. These workers used desiccated preparations from various parts of the human stomach in the treatment of this condition and showed that the intrinsic factor was produced in the human fundus and cardiac region, and not, as in the pig, in the pyloric region of the stomach. This explains many points which were previously obscure—e.g. why no intrinsic factor is present in duodenal secretion, and why pernicious anæmia is very rare after partial gastrectomy.

With regard to treatment, it is being generally recognised that although the typical cases—the vast majority—of pernicious anæmia in Britain do well on highly purified liver extracts, nevertheless a definite proportion of cases met with do not do well unless one of the more crude liver extracts is used. The proteolysed liver extract described by Davis, Davidson, Riding & Shaw (1943), and now commercially available, is of particular value in some of these resistant cases.

Dyke, Della Vida & Delikat (1942) have observed the tendency of patients with pernicious anæmia in wartime to relapse in the Spring. They concluded that this was due to lack of vitamin C, as they found that these patients could be maintained on the same dosage of liver extract if a supplement of vitamin C was given at the relevant season.

Anæmias of Pregnancy

Many papers have been published on this subject in the past few years in Britain and also in India and Africa. Elliot (1944) has recently proposed a classification of these anæmias in the light of his own and other findings. While no great advances in knowledge have been made, the following generalisations may be listed. The most common type of anæmia during pregnancy in any country would appear to be the hypochromic type, largely caused by a deficiency of intake of foodstuffs rich in iron. The macrocytic type appears to be more common in tropical than in non-tropical countries, but does occur in Britain, as the 80–100 cases recorded in the last two years show—e.g. Fullerton (1943), Miller & Studdert (1942). In most of these cases there has also been evidence of iron deficiency. The cause of the macrocytic anæmias is complex. In some cases there is a temporary failure of production of intrinsic factor in the stomach, as shown by Strauss & Castle (1933). In others a failure of intestinal absorption, or more frequently a dietary deficiency of extrinsic factor aggravated by vomiting or anorexia is present. Bethell, Gardiner & MacKinnon (1939) attribute some of the milder forms to low-serum proteins due to a protein-deficient diet and Chatterjee (1940) has found the blood cholesterol to be very low and reports benefit from intramuscular injections of cholesterol in olive oil. In some cases it appears that the macrocytosis is a "pseudomacrocytosis" and that the anæmia is due to an acute hæmolytic process.

In most cases, treatment with parenteral liver extract, particularly the less purified forms, rapidly brings about considerable improvement and the patient satisfactorily comes to term. Occasionally some cases become hypoplastic and need repeated transfusion. Iron also should always be prescribed.

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¹ [see BMB 453, 454 & 455]

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Hæmolytic Anæmias

It is now generally believed that only a very small percentage of cases of acquired acholuric jaundice are aberrant forms of the familial type. From acquired acholuric jaundice Dameshek & Schwartz (1940) and Singer & Dameshek (1941) have differentiated a group of cases under the heading "symptomatic hæmolytic anæmia," where a cause or at least a predisposing cause, such as carcinomatosis, Hodgkin's disease, etc., is present. This subject has been reviewed at length by Davis (1943), who has suggested a provisional classification of these anæmias. The term "acquired acholuric jaundice" is now usually replaced by the names subacute or chronic idiopathic hæmolytic anæmia. Most of these cases show macrocytosis, but erythrocyte fragility and microspherocytosis are variable.

Cases continue to be recorded of acute hæmolytic anæmia following various sulphonamides, but these are extremely few in relation to the number of patients treated. The prognosis is good.

The elucidation of hæmolytic disease of the newborn (erythroblastosis foetalis) has been the most outstanding hæmatological advance of recent years. The immunisation of an Rh-negative mother by an Rh-positive foetus, with later destruction of the foetal erythrocytes and damage to foetal tissues by the maternal anti-Rh antibodies so formed, is the most important cause of this disease. It must, however, be remembered that, extremely rarely, the ABO blood groups and other factors may be of ætiological significance. This subject is reviewed in more detail elsewhere,* so will not be further considered here.

Aplastic and Hypoplastic Anæmias

There is little doubt that these types of anæmia are becoming more prevalent. They constitute the most important members of the group of diverse conditions named "refractory anæmia" by Bomford & Rhoads (1941). Davidson, Davis & Innes (1943) have recently discussed a number of cases.

Many cases of aplastic or hypoplastic anæmia occur as the result of proven exposure to toxic substances, but the idiopathic type is becoming increasingly common. The treatment consists of two chief parts; first, the erythrocyte count is maintained at an adequate level by blood transfusions, which are repeated as often as necessary until the hypoplastic bone-marrow resumes its full hæmopoietic function. In this connection it is necessary to stress the importance of accurate cross-typing by the tube or other delicate method in order to detect the presence of any atypical antibodies produced in the patient's serum by the repeated transfusions. Secondly, it is usual to ensure the presence of adequate amounts of all the hæmopoietic factors by the administration of iron, liver, vitamin C and a diet containing plenty of good protein. In a certain percentage of cases after weeks, or even several months, the bone-marrow function may return to normal. If there is no improvement within six months, Whitby & Britton (1944) recommend splenectomy and record at least five successful results.

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³ [see BMB 439]

⁵ [see BMB 444]

⁹ [see BMB 441]

CLINICAL HÆMOGLOBINOMETRY

HAROLD SCARBOROUGH, M.B., PH.D.

Although the estimation of hæmoglobin is one of the oldest most commonly employed of all laboratory methods in clinical medicine, there can be few that are carried out with less precision. This is not entirely due to fundamental defects of the methods themselves, but often to technical carelessness, to inexact and sometimes grossly inaccurate apparatus, and to the lack of suitable agreed standards to which the results can be referred. Since the development of the Gowers hæmoglobinometer in 1878, modifications of this instrument have been in constant use and the results have hitherto been considered satisfactory for clinical purposes. In recent years, however, the determination of hæmoglobin has been used as an index of shock and in the assessment of nutrition. To satisfy these demands and those of a higher standard of hæmatological investigation, a greater degree of accuracy than was hitherto considered necessary has been required. This has led to an increased interest in the principles upon which the methods are based, upon the nature of the technical procedures involved, and upon the standards of normality to be adopted (*Medical Research Council*, 1943).

A method which is to prove generally useful in clinical medicine must combine accuracy with speed and simplicity. Methods based upon the iron content of blood or upon its oxygen capacity as well as those involving the use of complicated and expensive instruments must, therefore, be reserved for research purposes and for the standardization of apparatus. With the advent, in recent years, of the cheap photoelectric cell, however, certain types of photoelectric colorimeter such as those described by King (1942) and by Bell & Guthmann (1943) are likely to be more generally used. The benzidine method of Wu may have a special sphere of usefulness in that it is said to measure all forms of hæmoglobin in as small a quantity of blood as 0.001 cm.³ with an accuracy of $\pm 4\%$ (Bing & Baker, 1931; Bing, 1932). From 2–12% of the circulating hæmoglobin in apparently healthy persons may be present in an "inactive" form, probably as methæmoglobin (Ammundsen & Trier, 1939; Ammundsen, 1941), and as much as 5% may be combined as carboxyhæmoglobin in the blood of heavy smokers. Methæmoglobin and sulphæmoglobin are frequently found in the blood of patients to whom sulphonamide drugs have been administered. A suitable method should therefore include all these forms of hæmoglobin and should be applicable to small quantities of blood obtainable without venipuncture. By reason of the fact that the blood of infants contains a form of hæmoglobin whose oxygen dissociation curve differs from that of normal hæmoglobin (McCarthy & Popják, 1943) and which is "alkali-resistant" (Brinkman & Jonxis, 1935), the determination of hæmoglobin concentration in infants may present special difficulties.

A number of methods is available which fulfil many of these requirements. The basis of all of them is the colour of oxyhæmoglobin or of one of its derivatives and, accordingly, they all depend upon the Beer-Lambert law which implies that, if the thickness of a layer of a coloured solution is maintained constant, then the concentration is proportional to the colour (or the extinction coefficient). Before this law can be used as the basis of hæmoglobinometry, however, a standard is required with which the colour of the unknown solution may be compared. The ideal standard would be derived from pure crystalline human hæmoglobin but, as this has so far not been available, an indirect method must be used instead. This is a grave disadvantage and gives rise to a number of difficulties which cannot be discussed here. It may be said, however, that no completely satisfactory standard has yet been devised.

Colour Standards

i. *Oxyhæmoglobin*: The first hæmoglobinometer devised by Gowers (Gowers, 1878) employed a dilute solution of blood compared against a standard solution of picrocarmine. Because of the difficulty of the visual comparison of these colours, this method has been abandoned. It has been shown that the colours of solutions of oxyhæmoglobin are proportional to their concentrations over a range of dilution from 1 in 1 to 1 in 5,000 (Newcomer, 1919; Holiday, Kerridge & Smith, 1935), and recently such solutions have been used

with satisfactory results in photoelectric colorimeters such as those described by Holiday, Kerridge & Smith (1935) and by Bell & Guthmann (1943). These methods, however, do not include derivatives other than oxyhæmoglobin and may give fallacious results if the concentration of other hæm pigments is high.

ii. *Cyanmethæmoglobin* (Stadie, 1920): This method has been extensively studied by Drabkin & Austin (1935) and adopted by Evelyn & Malloy (1938) for photoelectric use. It includes methæmoglobin and is simple, easy and accurate. It is described by King, Gilchrist & Delory (1944) as "the method of choice for research purposes" but is unsuitable for clinical use by reason of the toxic reagent required—potassium cyanide.

iii. *Pyridine-hæmochromogen* (Rimington, 1942): This method possesses the great advantage that the standard is pure crystalline hæmin which is easy to prepare (Gattermann, 1934) and is available commercially.* It is, however, regarded as unsuitable by King, Gilchrist & Delory (1944) because the rate of colour development is not identical in the test prepared from blood and in the standard. All hæm pigments are included and the method is said to be rapid and precise when special apparatus is employed (Rimington, 1942). A satisfactory degree of accuracy for clinical purposes may, however, be achieved very simply by using a hand spectroscope as originally recommended by Roets (1940). The unpleasant smell of the pyridine will, however, be regarded by many as an insuperable objection.

iv. *Acid hæmatin*: Originally described by Sahli (1889), this method has become very popular because of its convenience. A large number of different instruments has been devised for making the colour comparison and there are almost as many artificial standards, many of which are unsatisfactory and all of which require independent standardisation. The method, though rapid and simple, is erratic and cannot be regarded as satisfactory. The acid hæmatin is not in true solution (Barcroft, 1928) and turbidity or actual precipitation may occur. The maximum colour is not developed for over 40 minutes (Newcomer, 1919) and the velocity of the colour reaction is not constant. These difficulties may be reduced by heating the solution (Ashford, 1943). Protein, lipid, bilirubin and other constituents of plasma affect the result (Wu, 1922). Furthermore the colours are not easily matched and the personal error may be as high as $\pm 10\%$ (Heilmeyer & von Mutius, 1938). Some of the difficulties of this method have been dealt with recently by Alstead (1940). The presence of carboxy- and methæmoglobin in the blood exerts a pronounced effect on the colour development. If arrangements for an acid hæmatin hæmoglobinometer to be standardised by the British Standards Institute should mature (*Medical Research Council*, 1943) some of the present anomalies may be removed.

v. *Alkaline hæmatin* (Wu, 1922): Recent work by Clegg & King (1942) shows this method to have considerable promise. It includes all hæm compounds (including sulphæmoglobin) and is not significantly influenced by constituents of the plasma since the strong alkali has a solvent action on protein and lipid. The alkaline hæmatin is in true solution. The colour, which is fully developed within 5 minutes in a boiling water bath, however, is not so deep as that of acid hæmatin (Ashford, 1943) and a colorimeter or photometer is desirable for matching against a standard prepared from crystalline hæmin. A dilution hæmoglobinometer of the Sahli type may, however, be adapted by substituting for the standard a tube of alkaline hæmatin (Clegg & King, 1942). In a recent investigation, King, Gilchrist & Delory (1944) found that on 20 normal bloods the standard deviations from iron analyses and oxygen capacity determinations respectively were—alkaline hæmatin 2.33 and 2.26%; cyanmethæmoglobin 1.25 and 2.18%; carboxyhæmoglobin (photometric) 1.70 and 2.49%; carboxyhæmoglobin (Haldane dilution tube) 3.02%.

vi. *Carboxyhæmoglobin* (Haldane, 1901; Palmer, 1918): This method is very widely used in Britain. Visual colorimetry is easier with this colour than with any other hæm

* [It may be obtained from British Drug Houses Ltd.]

pigment (*Medical Research Council*, 1943). Methæmoglobin and sulphæmoglobin are not measured, but the former may be included by preliminary reduction with sodium hydro-sulphite. One of the chief causes of the unreliability of values for hæmoglobin concentration lies in the survival of the dilution colorimeter which has long since disappeared from all other biochemical estimations. Dilution colorimetry lends itself to a high degree of personal error, and in the interests of speed, convenience and accuracy, should be replaced by a constant dilution method. However, in careful hands it is probably true that the ultimate limit of visual colour discrimination ($\pm 2\%$) can be reached with a Haldane-Gowers type of hæmoglobinometer (Donaldson, Harding & Wright, 1943). The standard in this type of instrument is a dilute solution of blood, with an oxygen capacity before dilution of 18.5 volumes per cent. by the Haldane method (1899) thoroughly gassed with CO (Donaldson, Harding & Wright, 1943). This standard is remarkably permanent, having been kept unimpaired for 4-5 years (Donaldson, Harding & Wright, 1943) or even for as long as 30-40 years (Donaldson, Harding & Wright, 1943; Plesch, 1941).

In order to obviate the difficulty of obtaining "standard" blood, the Haldane standard has now been defined in terms of colour on the Commission internationale de l'Eclairage (C.I.E.) trichromatic scale (1931), and this has resulted in the British Standards Institution (B.S.I.) specification B.S. 1079: 1942.* In addition, the forms of pipettes, dilution tube and colour tube have been accurately defined and may be standardized by the British National Physical Laboratory. The hæmoglobin equivalent of the B.S.I. Haldane colour standard has now been evaluated (Macfarlane & O'Brien, 1944; King, Gilchrist & Matheson, 1944) as equivalent to an oxygen capacity of 19.7 ± 0.2 ml. oxygen per 100 ml. blood and to an iron content of 49 ± 0.8 mg. iron per 100 ml. The definition of the standard in terms of colour, the standardization of all apparatus and the observations set forth in *Recommendations of standard methods for clinical determination of hæmoglobin* (*Medical Research Council*, 1943) should ensure a higher degree of accuracy in the determination of hæmoglobin concentration.

Photoelectric Methods

Although it has been stated that colour differences of 2% on the Haldane scale are just appreciable with a dilution colorimeter of the Haldane-Gowers type (*Medical Research*

Council, 1943), many clinical workers find it impossible to achieve this degree of accuracy. The sorts of errors which can occur in clinical practice with old and unstandardized apparatus have been reported on by Hay (1943). There can be no doubt that the further development of photoelectric methods offers the most hopeful line of advance for the assessment of the actual colour of the compound chosen and so for the concentration of hæmoglobin in solution. Many of the difficulties inherent in photoelectric estimations are overcome by using the Brice (1937) balanced circuit as described by Reeve (1944). Some of these difficulties have been referred to by Peterson & Strangeways (1944). It must be remembered, however, that the presence in the sample of different hæmoglobin compounds with differing absorption spectra may interfere with the direct relationship between light absorption and hæmoglobin concentration and, secondly, that other materials such as constituents of plasma, slight turbidity of the solutions, etc., may significantly affect the result. A simple, rapid and trustworthy photoelectric method for the determination of hæmoglobin has recently been described by Reeve (1944). By utilizing the total absorption of hæmoglobin and oxyhæmoglobin in the green, this method achieves an accuracy of $\pm 2\%$ hæmoglobin. If hæmoglobin pigments be converted into cyanhæmoglobin the procedure becomes more sensitive—a change of 0.5% can be detected with average care. The presence of relatively large amounts of sulphæmoglobin, which is not convertible to cyanhæmoglobin, affects the result, but the presence of such amounts is detected during the estimation.

Finally it should be mentioned that the practice introduced by Hayem of expressing the hæmoglobin concentration as a percentage of an arbitrary normal figure has led to much confusion by reason of the fact that concentrations of hæmoglobin varying between 12.4 and 17.3 g. per 100 ml. have been accepted as equivalent to 100%. The logical way to avoid this chaotic state is to express hæmoglobin values in terms of actual concentration without being committed to any arbitrary scale of normals. This "13.8 g. of hæmoglobin per 100 ml. of blood" is an accurate way of expressing a concentration of hæmoglobin which might be recorded as 111% on one scale and 80% on another.

Note

Testing of Haldane hæmoglobinometer colour tubes and graduated tubes

The *National Physical Laboratory* is prepared to accept hæmoglobinometer colour tubes and graduated hæmoglobinometer tubes for test of their conformity with the *British Standards Specification* (B.S. 1079: 1942). Full particulars of the tests and the fees charged may be obtained through the Editor of *BMB*.

* [Readers not resident in the United Kingdom who require a copy of this specification should apply to the Editor of *BMB*.]

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¹ [see *BMB* 470]

² [see *BMB* 469]

CIRCULATORY DYNAMICS OF HÆMORRHAGE

E. P. SHARPEY-SCHAFFER, M.R.C.P.

It is now generally agreed that hæmorrhage is the major factor requiring treatment in casualties with low blood-pressure. Studies of circulatory dynamics after hæmorrhage

in man, as opposed to the experimental animal, are of special interest, for it appears that there may be some species-difference, for example, in the time taken for the restoration of

blood volume. In man, dilution of hæmoglobin and restoration of blood volume after bleeding is slow (Ebert, Stead & Gibson, 1941; Wallace & Sharpey-Schafer, 1941). Further, new methods are becoming available for study of circulatory dynamics which are particularly applicable to unanæsthetised man.

Methods

Blood-volume determination continues to present a difficult problem. Using the Evans-blue method, Morris (1944) points out that hæmolysis in the plasma samples interferes with the analysis, as hæmoglobin is converted by the extraction process into a pigment which has a significant light absorption in the same spectral region as Evans-blue. He describes an optical method for correction of this error. Dyson, Plaut & Vaughan (1944) made observations on the changes in erythrocytes, hæmoglobin, mean corpuscular volume, serum protein and plasma volume in a two-hour period following the removal of 540 cm.³ of blood in 8 normal subjects and following transfusion of concentrated erythrocytes in 8 anæmic subjects. Plasma volume was estimated by the Harington, Pochin & Squire (1940) modification of the Evans-blue method of Gibson & Evans (1937). They found a considerable variation in the response of different individuals. In one instance the plasma volume after bleeding was that calculated; in the others dilution or overdilution were noted. Plasma proteins showed either no change or a fall. The data after concentrated corpuscle transfusions suggested that there might either be a small increase in plasma volume (442 cm.³ to 262 cm.³) above that calculated or else a small decrease (241 cm.³ to 253 cm.³). The authors consider that in estimating the amount of fluid that has passed from the tissues into the circulation, the amount absorbed by the erythrocytes is significant and must be taken into account.

McMichael, Sharpey-Schafer, Mollison & Vaughan (1943) measured the blood volume in severe anæmia by a concentrated corpuscle-hæmoglobin method (Hill, 1941) according to the formula: Blood volume (cm.³) = $\frac{V(Hb_v - Hb_1)}{Hb_2 - Hb_1}$

where V cm.³ = the volume of concentrated corpuscles injected (usually about 500 cm.³), Hb_v = hæmoglobin percentage of injected corpuscles, Hb₁ = hæmoglobin percentage of patient before transfusion, and Hb₂ = hæmoglobin percentage after transfusion. Hæmoglobin was estimated by a photoelectric method. In 7 cases, simultaneous estimations were made by a concentrated-corpuscle-differential glutination method, and in 3 by the Evans-blue dye method. Results agreed within $\frac{1}{2}$ litre. The concentrated-corpuscle-hæmoglobin method can be used only in severe anæmia.

States of low blood-pressure can be analysed on the principle: mean blood-pressure = cardiac output per unit time \times total peripheral resistance. It is now possible to make accurate serial estimations of cardiac output in man by the method of cardiac catheterisation. First used by Forssmann (1929) and later by de Carvalho & Moniz (1933) and Ameuille, Ronneaux, Hinault, Desgrèz & Lemoine (1936), this technique was developed by Cournand & Ranges (1941) for measuring cardiac output by a direct Fick method. The procedure is simple and safe. It consists, essentially, of passing a radio-opaque gum-elastic ureteric catheter along the veins of the arm into the right auricle, where the position of the tip is checked by x-rays. The pressure in the right auricle can be recorded by a citrate or saline manometer, and the oxygen unsaturation of mixed venous blood can be measured by withdrawing suitable samples under oil. Details of the procedure are given in the papers of Cournand and his colleagues and by McMichael & Sharpey-Schafer (1944). Over 500 cardiac catheterisations have now been performed without complication.

Factors Affecting Cardiac Output in Normal Subjects

Results obtained in normal subjects (McMichael & Sharpey-Schafer, 1944) were those to be expected from the well-known work of Starling and of Wiggers (1927). Reduction of the right auricular pressure by bleeding caused a fall in cardiac output, and raising the right auricular pressure by rapid transfusion caused a rise. Accelerating the heart by intravenous injection of atropine usually caused an increased cardiac output. However, there was also a fall in right auricular pressure, and this was sometimes sufficient to counteract the usual increase of output on acceleration. Intravenous adrenaline in doses that did not raise the blood-

pressure or accelerate the heart (under 10 µg. per minute) increased cardiac output, presumably by a direct action on the heart itself. Cardiac output in the supine posture showed an average increase of 33 % over that in the erect subject.

Immediate Effects of Hæmorrhage

Apart from its importance in the "shock" problem, a sudden fall of blood-pressure after bleeding has been of particular interest to transfusion units. Poles & Boycott (1942) found that 3.8 % of young factory workers fainted after removal of 440 cm.³ of blood, and 8.5 % fainted after removal of 540 cm.³ They thought that the incidence of fainting was raised by bleeding tired and hungry subjects. Glucose (40 g.) given prophylactically was without effect, but 1 litre of saline before bleeding seemed to be beneficial in men from hot workshops. In a report to the *Medical Research Council* by a sub-committee of the Blood Transfusion Research Committee (*Medical Research Council*, 1944) an analysis of data was given from 362 blood donors who had fainted. The results showed that the incidence of fainting was lower in men than in women, but there was no evidence that age, length of wait at the centre, difficulties in bleeding or menstruation had any effect on the incidence of fainting. The most striking finding was that a high proportion of fainters gave a history of fainting either at a previous donation or on some other occasion. Loutit, Mollison & van der Walt (1942) were able to confirm previous work in showing that venesection lowered and transfusion raised the peripheral venous pressure. They found little change in blood-pressure and heart-rate in 20 donors bled of 430 cm.³ However, with larger venesections (up to 1100 cm.³) the incidence of acute fall of blood-pressure and bradycardia ("faint") was much higher (Wallace & Sharpey-Schafer, 1941). By placing venous tourniquets on the thighs for 20 minutes at diastolic pressure, or better at 10 to 15 mm. Hg. below systolic pressure, and then bleeding 500 cm.³ or more, a very high incidence of fainting can be produced in normal volunteers. This procedure is probably equivalent to a venesection of about 1400 cm.³, and has the advantage that release of the tourniquets will rapidly restore blood-pressure and consciousness if the faint is severe. Using such large venesections in normal male volunteers in the supine position Barcroft, Edholm, McMichael & Sharpey-Schafer (1944) studied the physiology of post-hæmorrhagic fainting by observing cardiac output (cardiac catheterisation) and forearm flow (Lewis and Grant plethysmograph). During the bleeding, blood-pressure was maintained but right auricular pressure and cardiac output fell steadily, indicating that while blood-pressure was kept at a normal level by increasing total peripheral resistance (probably vasoconstriction in skin and splanchnic areas), yet there was no corresponding increase of venous tone to maintain right auricular pressure. The acute fall of blood-pressure and bradycardia (fainting) were not due to any further fall in cardiac output but to a sudden great decrease in total peripheral resistance. During the faint, forearm flow was approximately doubled when the blood-pressure was halved, indicating great arteriolar vasodilatation in forearm muscles, since the skin is pale during the faint. If the rest of the skeletal muscle behaves like the forearm, then vasodilatation in muscle may explain the fall of blood-pressure in post-hæmorrhagic fainting. Barcroft & Edholm (1944) have further shown that this vasodilatation is mediated by vasomotor nerves. On the afferent side it is possible that the fall of pressure in the right auricle may be a trigger mechanism. Retransfusion immediately restored forearm flow and blood-pressure to normal. In two cases intramuscular methedrine (30 mg. N-methyl amphetamine) restored blood-pressure by increasing total peripheral resistance; this substance can also be given intravenously.

Late Effects of Hæmorrhage

Data are still scanty on the phase of "shock" after hæmorrhage. This is the phase of low blood-pressure, with normal or increased heart-rate, which is commonly seen in the wards after spontaneous bleeding and responds well to transfusion. The evidence of Cournand and his colleagues indicates that low right auricular pressure and low cardiac output are the main factors causing low blood-pressure. In some of their cases total peripheral resistance was increased, and in others cardiac output was not as low as might be expected. Oxygen consumption might be slightly reduced but arterial oxygen-saturation was normal; there seems little

purpose, therefore, in giving oxygen. At the present time Courmand and his colleagues think that pressor substances should not be used, as vaso-constriction is probably already optimal in this phase, and that hyperventilation should not be depressed with morphine. It seems probable that the "faint" may supervene on the "shock" phase if any procedure, such as a change to the sitting or upright posture, further reduces right auricular pressure.

In the course of spontaneous recovery from a large hæmorrhage, the circulation often enters a third phase which may be termed the "hyperkinetic syndrome" (Harrison, 1939). Estimation of blood volume in post-hæmorrhagic and chronic anæmia with normal systolic blood-pressure showed surprisingly low figures, often as low as 2 litres (McMichael *et al.*, 1943). Further work (Sharpey-Schafer, 1944) showed that the normal or slightly raised resting oxygen supply in severe anæmia was maintained by three main factors (i) increased cardiac output, (ii) increased utilisation of available arterial oxygen, (iii) diminished blood volume resulting in greater concentration of total circulating hæmoglobin. Increased cardiac output could be due to a moderate increase of heart-rate combined with a normal or raised venous pressure. In the most severe cases the right auricular pressure was elevated, sometimes to high levels. This rise of venous pressure or "heart failure" was thought to be the result of an adjusting mechanism, perhaps increased venous tone, which served to maintain the necessarily high cardiac output.

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¹ [see BMB 477]

² [see BMB 479]

³ [see BMB 478]

⁴ [see BMB 481]

⁵ [see BMB 476]

It is clear that a circulatory phase in which the blood volume is low, and the venous pressure and cardiac output are increased, is likely to give trouble when further overloaded by transfusion. Drummond (1943) has recorded some excellent clinical examples; three of his five cases had hæmoglobin levels of 25 % or less and all appear to have developed pulmonary œdema, in one case after as little as 110 cm.³ of blood. The three patients who died had well-marked pulmonary œdema, and there was great ballooning of the right auricle in a patient who had received about 2½ litres. When more exact studies are made it is found that, in severe anæmia, raising the right auricular pressure further by a transfusion may have precisely the opposite effect to the same procedure in a normal subject. Instead of increasing cardiac output, as in the normal, it causes a decrease. The situation seems in every way comparable to Starling's overloaded heart-lung preparation. Patterson & Starling (1914) showed that increasing the venous pressure caused a corresponding increase in cardiac output, until a point was reached after which further increase of venous pressure caused a fall in output.

At the present time the evidence indicates that, following hæmorrhage, venous pressure changes are of considerable importance both in the process of spontaneous recovery and in assessing the effects of transfusion. If more accurate methods of measurement are not available, clinical observation of the neck veins by the well-known methods described by Sir Thomas Lewis may give valuable information.

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REVIEW OF SELECTED PAPERS

Blood Groups

426

THE Rh FACTOR AND ERYTHROBLASTOSIS FETALIS: AN INVESTIGATION OF 50 FAMILIES

by R. R. Race, G. L. Taylor, D. F. Cappell & M. N. McFarlane, *British Medical Journal*, 2, 289-293, 4/9/43

Workers from the Medical Research Council Serum Unit and from the University of St. Andrews have collaborated in the investigation of 50 families in which erythroblastosis foetalis, better called hæmolytic disease of the newborn, has been diagnosed. The cases were collected in many parts of Great Britain and Northern Ireland, and in those reported it seemed reasonably certain that the diagnosis was correct. An attempt was made to determine the ABO and Rh blood groups of parents and surviving children and to get details of all pregnancies and their outcome. The authors point out that although the material is far from complete, much information has been gathered together and some of it may well prove of value to future workers. The details relating to the families are tabulated.

Of the 50 mothers, 6 were Rh-positive and 44 Rh-negative, and in the sera of 38 of the Rh-negatives, anti-Rh agglutinins were found. These figures agree well with those of other workers and confirm Levine's theory that iso-immunization of the mother plays an important part in the ætiology of

hæmolytic disease of the newborn. Anti-Rh was not found in 6 of the Rh-negative mothers, but the fact that 6 of the 12 mothers in whose serum anti-Rh was not found were Rh-negative strongly suggests that Rh was concerned.

In one pregnancy in ten the mother is Rh-negative and the baby Rh-positive, and in one pregnancy in five the mother has an agglutinin for an ABO antigen present in her foetus, but the disease is much rarer [1 in 200-400 pregnancies] than it would be if it occurred whenever the blood-group situation makes it possible. Other factors yet unknown must be involved.

When the mother is Rh-positive (or even Rh-negative), other erythrocyte antigens than Rh may perhaps cause the disease. The husbands of only 2 of the 6 Rh-positive mothers were grouped. One was O, Rh-negative; the other A, Rh-negative. After the investigation of the 50 families had been made, the next two husbands of Rh-positive mother cases examined were negative and positive. It appears significant that three of four husbands of Rh-positive mothers with affected children should be Rh-negative. The family in which both parents were Rh-positive produced St serum and is described at length by McCall, Race & Taylor (1944). Families in which the diagnosis is wrong will most commonly be included amongst those with Rh-positive mothers, simply because six out of seven mothers in the population are Rh-positive.

Not one Rh-negative child was found amongst the offspring

of the Rh-negative mothers; 33 healthy and 16 affected children were tested. The absence of negative children from the healthy group is highly significant and may be due to most of the fathers being homozygous (RhRh) and producing only Rh-positive children. Immunization is more likely when an Rh-negative mother has a positive foetus every pregnancy than when some may be positive and others negative, as with a heterozygous (Rhrh) husband. Although negative children do occur in affected families, the scarcity has to be considered in estimating the chances of getting a negative (an unaffected) child in future pregnancies. In the 50 families, with one exception, no mother who had once produced an affected baby ever had a later normal surviving child.

Of the first children borne by the 44 Rh-negative mothers 38 were unaffected, five were stillbirths or miscarriages and one suffered from the disease. From the second birth onwards there was a steadily increasing ratio of affected to normal children. Four of the six Rh-positive mothers, on the other hand, had first children who were affected, two being stillbirths. The earlier onset in this group might be due, if the ABO groups were responsible, to the iso-agglutinins being already present in the maternal serum.

About a quarter of the affected children survived; three-quarters were born dead or died mostly within a week of birth. Affected children were approximately evenly distributed between the two sexes.

REFERENCE

¹ McCall, A. J., Race, R. R. & Taylor, G. L. (1944) *Lancet*, 1, 214
¹ [see BMB 431.]

427

HÆMOLYTIC DISEASE OF THE NEWBORN (ERYTHROBLASTOSIS FŒTALIS): ITS TREATMENT WITH RHESUS-NEGATIVE BLOOD

by J. D. Gimson, *British Medical Journal*, 2, 293-297, 4/9/43

The author reports in much detail a series of 19 consecutive cases of hæmolytic disease of the newborn collected during ven months at the *Hospital for Sick Children*, Great mond Street, London. The cases are typical of those ming to a children's hospital which is not part of a maternity spital, and are necessarily selected, for macerated foetuses d stillborn infants will never be seen, and hydrops foetalis icterus gravis—fatal within 24 hours—will be admitted ly rarely. All the mothers were Rh-negative and all the ants Rh-positive, and anti-Rh was found in the sera of all but one of the mothers. Some cases, even of icterus gravis, recover without treatment, but the mortality seems to be about 80 %.

Knowledge of the connection between iso-immunization of the mother and hæmolytic disease of the newborn has suggested the treatment of the child by the transfusion of blood lacking the antigen for which the mother has made the agglutinin. Attempts to replace by transfusion the baby's blood lost by lysis have in the past not been very successful, because in most cases Rh is involved. As six donors out of seven are Rh-positive and their blood would not have been Rh-tested, Rh-positive blood would usually have been given, and this, like the baby's own, was liable to be destroyed.

Eighteen of the 19 babies, whose ages on admission varied between three days and six weeks, were transfused with Rh-negative blood free from anti-Rh. It was rarely thought necessary to transfuse unless the erythrocyte count was below 3.5 millions.

All the babies received Rh-negative blood, and some of the earlier ones were given Rh-positive blood as well; but, although the positive blood caused an initial rise in hæmoglobin and erythrocytes, hæmolysis continued, and within a few days further transfusion was needed. Rh-negative blood does not prevent hæmolysis of the child's own cells, it merely provides cells which will not be destroyed more rapidly than normal, and on which the child may live until the lytic process ends. When a mixture of Rh-positive and Rh-negative blood was given the negative cells survived normally while the positive were often destroyed within a few days. In 14 of the 18 cases the results are described as "perfect"; the other 4 regained and maintained normal blood pictures. No more than two transfusions of negative blood were needed in any case.

The author shows how encouraging are the results in this series by comparing them with those from a series of 17 consecutive cases treated in the same hospital with blood which, untested for Rh, would nearly always be Rh-positive. Six of the 17 died from the disease or from transfusion; 4 were kept alive but without improvement in the blood condition; and in only 7 were the results satisfactory, although they received much more blood—up to six transfusions in some cases—than the 18 babies treated with Rh-negative blood. Moreover, no reactions followed the giving of negative blood, but in the other series there was more often than not a rise of temperature and some constitutional disturbance with increase of jaundice and size of liver and spleen.

The transfusions were given intravenously, by drip into the internal saphenous or a cubital fossa vein. An attempt was made to maintain a constant rate of 15 to 20 cm.³ per hour. The infants were kept in hospital overnight after the transfusion. The volume of blood to be given was calculated in cm.³ from the formula

$$\frac{\% \text{ rise of Hb required}}{100} \times \text{blood volume}$$

the blood volume being approximately 88 cm.³ per kg. body weight calculated on expected weight for age from birth-weight. The author concludes that if an infant with hæmolytic disease of the newborn lives long enough to reach hospital there is a good chance of its survival. She thinks it unlikely that the dreaded kernicterus can be avoided.

428

OCCURRENCE OF THE Rh ANTIGEN IN THE POPULATION: NOTES ON 5 CASES OF ERYTHROBLASTOSIS FŒTALIS

by E. D. Hoare, *British Medical Journal*, 2, 297-298, 4/9/43

The author, working in the Welsh National School of Medicine, immunized 10 guinea-pigs with Rhesus monkey blood as described by Landsteiner & Wiener (1941). Three of the immunized animals yielded sera which, at dilutions up to 1:60, gave a clear distinction between Rh-positive and Rh-negative bloods. By tests made with these sera it was found that the distribution of the Rh-positive and Rh-negative persons in South Wales agrees with that found in England and amongst the white people in the United States of America. The Welsh results were:

Group	AB	A	B	O	Total
Rh-positive	27	349	90	483	949 (84.6 %)
Rh-negative	3	64	14	92	173 (15.4 %)

Five cases of erythroblastosis foetalis are reported, in all of which the father and child were Rh-positive whilst the mother was Rh-negative. Anti-Rh was found in the sera of the five mothers. In one of the sera the agglutinin seems to have been undetectable at 37° C.; it was found at room temperature in the undiluted serum and to a titre of 1:4 at 0° C. Four of the children were transfused with blood which was not tested for Rh: only oge of them lived. The fifth child died without transfusion. These cases occurred before the need of treatment with Rh-negative blood had been realised.

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429

THE SURVIVAL OF TRANSFUSED ERYTHROCYTES IN HÆMOLYTIC DISEASE OF THE NEWBORN

by P. L. Mollison, *Archives of Disease in Childhood*, 18, 161-172, December 1943

This paper is a report to the *Medical Research Council* from the South-West London Blood Supply Depot, and records the first direct observations of the survival of transfused blood in the circulation of babies with hæmolytic disease of the newborn. Eighteen babies suffering from this disease were transfused with Rh-negative blood and 10 of them were given Rh-positive blood as well, either at the time in a mixture or consecutively. The survival of each type of donor's erythrocytes was followed by a very ingenious modification of the Ashby (1919) technique. An example is

given: a baby OM Rh-positive was transfused with a mixture in known proportions of OM Rh-negative and ON Rh-positive blood. After transfusion the baby's blood was agglutinated by anti-Rh serum, the unagglutinated cells being those of the first donor, and these were counted. The baby's blood was next agglutinated by anti-M serum; this time the unagglutinated cells were those of the second donor and could also be counted. Corrections have to be made for the number of cells failing to be agglutinated by their homologous serum.

The results were conclusive and fully confirmed the correctness of the theoretical expectation and of the clinical impressions. If Rh-positive blood was given in the first fortnight of life it was practically all eliminated within ten days (in 3 cases elimination was complete in three days). If the baby was older, Rh-positive blood was tolerated better. Compared with this, 90 % of the Rh-negative transfused cells were still surviving at the end of a week, and their total survival was about that of compatible transfused cells in the adult.

The author therefore considers that when an infant with hæmolytic disease of the newborn has to be transfused, Rh-negative blood of its own group should be given when serological tests have been made and it is fairly certain that destruction is due to anti-Rh agglutinins. O Rh-negative blood is recommended when no tests have been made, and O blood should be used when destruction is thought to be due to anti-A or anti-B agglutinins. When destruction is due to agglutinins other than typical anti-Rh, O blood compatible with the mother's serum is probably the safest. In every case direct matching of the donor erythrocytes against the mother's serum seems a desirable precaution before transfusion.

An interesting additional observation is recorded which may be of physiological importance. One baby expected to suffer from hæmolytic disease of the newborn was transfused at birth, while its Rh grouping was being done. The baby was Rh-negative, however, so the transfusion was stopped, 80 cm.³ having been given. Two days later the hæmoglobin was over 150 % (Haldane), and it was still 134 % 10 days after birth. During these 10 days there was not the slightest tinge of jaundice. The author considers that this calls in question the generally accepted theory that physiological jaundice results from a process designed to destroy the excessive numbers of erythrocytes needed *in utero* but unwanted in the open air.

REFERENCE

Ashby, W. (1919) *J. exp. Med.* 29, 267

430

HÆMOLYTIC DISEASE IN THE NEWBORN: THE Rh FACTOR

by F. A. Langley & F. Stratton, *Lancet*, 1, 145-148, 29/1/44

This is a review of the clinical, pathological and serological findings in 23 carefully investigated cases of hæmolytic disease of the newborn. Twenty-two of the mothers were Rh-negative and anti-Rh was found in the serum of 19 of them.

As a control, 41 cases of physiological jaundice were also examined. The number of Rh-negatives (5) amongst the mothers of these controls was close to that expected in a random sample of women. This suggests that when the cases are carefully diagnosed Rh is seldom found to be the cause of physiological jaundice. However, one of the five Rh-negative mothers had anti-Rh in her serum.

The authors point out the difficulties that may be met in making a diagnosis of hæmolytic disease, since important indications such as jaundice or erythroblastæmia may be absent. In their experience "the most important single clinical feature was a progressive fall in the hæmoglobin level below that normally expected." Post-mortems were performed on twelve of the babies and the findings are reviewed.

Some interesting points of technique are mentioned. First and most important, the authors do not consider high-titre human anti-A and anti-B serum adequate for the ABO grouping of babies. Immune rabbit sera were much more satisfactory in their experience.

There is a good description of a certain type of clumping familiar to Rh workers which must not be confused with true

agglutination. These clumps are due to gentle handling of sedimented cells and were described as "large almost circular clumps shedding cells as they moved, which gave them a comet-like appearance."

The authors were able to demonstrate anti-Rh agglutinin in the milk of 7 out of 9 mothers who were known to have the antibody in their serum.

431

RHESUS ANTIBODY IN Rh-POSITIVE MOTHER CAUSING HÆMOLYTIC DISEASE OF NEWBORN

by A. J. McCall, R. R. Race & G. L. Taylor, *Lancet*, 1, 214-215, 12/2/44

In this paper are given the clinical details and history of the family of the Rh-positive mother from whom was obtained the antiserum St which has proved of fundamental importance in the recognition of allelomorphs of the Rh gene and resulting genotypes. Investigation of this unusual serum, from an Rh-positive mother, yet capable of agglutinating most Rh-positive cells, showed that it was similar to, but not necessarily identical with, the anti-Hr discovered by Levine and his colleagues in America. St serum reacts with 80 % of people including all Rh-negatives, all heterozygotes (Rhrh) and some of the homozygotes (RhRh). These reactions are due to the presence in the erythrocytes of antigens determined by allelomorphs of the Rh gene. The use of St with other forms of anti-Rh sera has made it possible to determine serologically the genotype of about 80 % of people. The genotype testing has been described in previous papers (Race & Taylor, 1943; Race, Taylor, Boorman & Dodd, 1943; Race, Taylor, Cappell & McFarlane, 1944).

A male infant in whom increasing jaundice had been noticed from the 2nd day was admitted to hospital on the 14th day with pallor, deep jaundice and a moderately enlarged liver. The stools and urine were deeply bile-stained. Hb 55 % (9 g. per 100 ml.), erythrocytes 2,500,000 per mm.³, colour index 1.1, mean diameter of erythrocytes 8.1 μ , leucocytes 15,000 per mm.³ Anisocytosis and polychromasia well marked; 300 normoblasts per mm.³; blood group O, Rh-positive. On the 16th day the Hb was 42 %. The mother was not available for testing, so 150 ml. of Rh-negative blood was transfused. The mother proved to be Rh-positive, and her serum contained a powerful agglutinin which acted on the cells of the Rh-negative donor used to transfuse the baby and on all of 12 unselected group O bloods. Agglutination occurred at room temperature but was stronger at 37° C. No agglutinin for these cells was found in the child's serum.

On the 22nd day Hb was 68 % and on the 27th 46 %. Of 20 group O bloods examined, the mother's serum failed to agglutinate 3, either at 37° C. or at room temperature. Transfusion of 200 ml. of blood from one of the 3 St-negative donors raised the Hb to 79 %, a level which was maintained, and the child was discharged free from jaundice on the 57th day.

The mother, who suffered from a severe hypochromic anæmia aggravated by post-partum hæmorrhage, was transfused with 600 ml. of St-negative group O blood without reaction.

Family history: Mother had had no stillbirths or abortions.

1st child, male, 1939. Healthy, no history of erythroblastosis.

Group ON, P-, Rh+, St+ (Rh₁rh).

2nd child, male, August 1941. Died from erythroblastosis. No investigations.

3rd child, male, January 1943. History given above. Group OMN, P-, Rh+, St+ (Rh₁rh).

Mother. Group OMN, P-, Rh+, St- (Rh₁Rh₁).

Father. Group A₁MN, P?, Rh+, St+ (Rh₁rh).

St serum does not react with Rh₁, and the father and children (all Rh₁rh) are St+ because they possess the recessive gene rh. The mother (Rh₁Rh₁), not having rh, was immunized by the child's rh. St always reacts with rh both in the heterozygous Rhrh and in the Rh-negative rhrh. St also reacts with Rh₂ [and with Rh^{*}, Rh₀ and Rh₃].

[In transfusing the baby and its mother with compatible St-negative blood the hospital pathologist (McCall) handled in a masterly fashion a new and unknown Rh blood-group situation.]

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THE INCIDENCE OF HÆMOLYTIC DISEASE OF THE FŒTUS ("ERYTHROBLASTOSIS FŒTALIS") IN DIFFERENT FAMILIES: the Value of Serological Tests in Diagnosis and Prognosis

by K. E. Boorman, B. E. Dodd & P. L. Mollison, *Journal of Obstetrics and Gynaecology of the British Empire*, 51, 1-23, February 1944

This paper reports on a large amount of work on hæmolytic disease of the newborn done at the South-West London Blood Supply Depot.

The authors applied certain pathological criteria before they accepted the diagnosis of hæmolytic disease. The results are given of the serological investigation of the 100 families that qualified. Of the mothers 97 were Rh-negative, and 93 of these had anti-Rh in their serum. Of the 3 Rh-positive mothers 1 had the anti-Rh₂ agglutinin and the other 2 had anti-B agglutinins of unusual strength, to which the authors attributed the hæmolysis. This suggests that, when the diagnosis of hæmolytic disease is made with certainty, anti-Rh is responsible for an even higher proportion of cases than was thought before, almost all of them in fact.

The titre of anti-Rh agglutinin was measured at intervals throughout 7 pregnancies. In 2 the titre rose and in 3 remained steady before the birth of an affected child. In 2 it remained steady and Rh-negative children were born. The authors usually found a rise of titre after delivery, 8-20 days post-partum being the peak and the favourable time to search for agglutinins.

A group of 60 infants with physiological jaundice was investigated. Six of their mothers were Rh-negative and 54 Rh-positive, figures which suggest that Rh plays but little part in this type of jaundice. However anti-Rh was found in the serum of three of the six mothers. One of these mothers had previously had a child which suffered from hæmolytic disease, so it is likely that the jaundice of the present infant was not physiological. There was no excess of hetero-specific pregnancies on the ABO system in this group. The authors conclude: "There is, therefore, no evidence that 'physiological jaundice' of the newborn is, in the great majority of cases, in any way connected with the presence of incompatible agglutinins in the mother's serum."

The diagnostic value of serological tests when hæmolytic disease is suspected is summed up thus: (i) The diagnosis is very probable when the mother is Rh-negative and has anti-Rh in her serum, or when she is Rh-positive and has any other atypical agglutinin acting on her baby's cells at 37° C. (ii) The diagnosis is less probable when the mother has very strong anti-A or anti-B agglutinins incompatible with her baby's cells, or when the mother is Rh-negative but no anti-Rh can be found. (iii) The diagnosis is improbable when the mother is Rh-positive and there is no atypical agglutinin in her serum, or when her anti-A and anti-B are not excessively strong.

Concerning the value of serological tests in prognosis, it is pointed out that the main importance of routine Rh tests in pregnancy is to ensure that Rh-negative women will not be given Rh-positive blood should they be transfused. In families in which hæmolytic disease has already occurred the prognosis is made less gloomy if the father can be shown to be heterozygous by finding an Rh-negative amongst the children. [The direct testing for homozygosity was hardly developed when this paper was written.] In all cases where anti-Rh is found in the mother's serum arrangements should be made to have Rh-negative blood ready for both mother and baby.

There is also a discussion on the possible parts played in this disease by the three factors, titre of maternal agglutinin, placental permeability and amount of extracorporeal group-specific antigen.

433

HÆMOLYTIC DISEASE OF THE NEWBORN: THE PREPONDERANCE OF HOMOZYGOUS Rh-POSITIVE FATHERS

by G. L. Taylor & R. R. Race, *British Medical Journal*, 1, 288-289, 26/2/44

The results reported in this paper from the *Medical Research Council Serum Unit* confirm the suggestion made by Race, Taylor, Cappell & McFarlane (1943), that there is a

preponderance of homozygous (RhRh) fathers in families affected by hæmolytic disease of the newborn. An Rh-negative woman is more liable to be immunized when every pregnancy is Rh-positive and provides the antigenic stimulus, as happens with a homozygous husband, than when he is heterozygous (Rh₁rh) and some children may be positive and others negative. About 3 out of 7 Rh-positive males are homozygous and 4 heterozygous.

All bloods which are not agglutinated by St serum * are homozygous RhRh and are about half of all the homozygotes. As 18 St-negatives were found amongst the husbands of 46 Rh-negative mothers with sera containing anti-Rh agglutinins and children suffering from erythroblastosis fœtalis, the authors estimate that 36 husbands were homozygous and 10 heterozygous, instead of the 20 homozygotes and 26 heterozygotes expected in a random sample of 46 Rh-positive people.

By serological tests (Race & Taylor, 1943; Race, Taylor, Boorman & Dodd, 1943; Race, Taylor, Cappell & McFarlane, 1944), the Rh genotypes of some of the husbands were determined, and further evidence of the predominance of homozygous fathers was obtained. Thus, of 38 husbands, only 5 were Rh₁rh and 33 not Rh₁rh, instead of the expected 15 and 23. About 33% of people are of the genotype Rh₁rh—that is about 40% of Rh-positives, and the shortage of this commonest type of heterozygote is highly significant. More complete genotype tests were made on 18 of the husbands and it was shown that at least 13 were homozygous instead of the 7 expected in 18 Rh-positive people.

This predominance of homozygous fathers affects very greatly the chances that Rh-negative, and therefore unaffected, children will be borne by Rh-negative mothers who have already had affected children. The genotype of about three-quarters of Rh-positive people can be determined serologically, and unless it can be shown serologically, or by his having an Rh-negative child or parent, that the husband is heterozygous, the prognosis is very poor.

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- ¹ [see *BMB* 426]

434

ERYTHROBLASTOSIS FŒTALIS

by J. R. Gilmour, *Archives of Disease in Childhood*, 19, Part I: 1-11; Part II: 12-20; Part III: 21-25, March 1944

In these three papers from the Bernhard Baron Institute of the London Hospital the author describes in detail the macroscopic and microscopic findings in 52 fatal cases of erythroblastosis fœtalis. The papers include a comprehensive survey of previous literature.

The author classifies the present series into 3 types, described as (i) hydrops fœtalis (24 cases); (ii) icterus gravis (26 cases); (iii) congenital anaemia (2 cases). Evidence is given that the three types are varieties of a single disease.

There is a brief discussion at the end of the third paper of the relationship between erythroblastosis and the Rh factor. Nineteen excellent photomicrographs are reproduced.

435

AN 'INCOMPLETE' ANTIBODY IN HUMAN SERUM

by R. R. Race, *Nature*, 153, 771-772, 24/6/44

The discovery of an "incomplete" antibody in certain anti-Rh sera indicates that there is still much to be learnt about this versatile system of antigens and antibodies. By an incomplete antibody is here meant one which will combine with its specific antigen on the erythrocyte, but which is not a suitable partner for the agglutination stage.

Human anti-Rh serum of the type called by Wiener "standard" agglutinates erythrocytes of the gene Rh₁ and also those of Rh₂. Anti-Rh₁ serum agglutinates the former

* [see *BMB* 431.]

but not the latter. If, however, cells of the genotype Rh₂Rh₂ or Rh₂rh are suspended in anti-Rh₁ serum, which causes no agglutination, and after a few minutes are separated from this serum, washed and re-suspended in saline, then these treated cells can no longer be agglutinated by standard anti-Rh serum. These treated cells are agglutinated as well as ever by anti-Rh₂ serum and by St serum. In other words only one of the three antigens which must be present on Rh₂ cells is being blocked, and the other two are left free and ready for agglutination. This interpretation was supported by absorption experiments. The inhibited antigen is that which would normally react with the standard anti-Rh antibody, and the author considers the inhibiting agent to be an incomplete form of this antibody.

Five out of six anti-Rh₁ sera contained the incomplete antibody in good strength, the sixth in weak but definite amount. One standard anti-Rh serum contained the incomplete as well as the complete form of the antibody. In such a natural mixture, or in one artificially made, the incomplete antibody wins the race for antigen when erythrocytes are added, and the expected agglutination does not occur.

A brief account is given of R. A. Fisher's formulation of the relationships found in the rhesus factor.

436

SYMPTOMLESS INCOMPATIBLE TRANSFUSION AND RESULTANT CHANGES IN ISO-AGGLUTININ TITRE

by R. Drummond, *British Medical Journal*, 1, 483-485, 8/4/44

Incompatible blood transfusions in which studies of iso-agglutinin titres have been made are not numerous. In this paper the Transfusion Officer of the Welsh Board of Health reviews the cases reported previously and records another.

The agglutinogens of the ABO system of blood groups are regularly antigenic for man, and when cells containing A or B are transfused into a recipient whose serum contains the corresponding agglutinin, there is usually an initial fall in the strength of the agglutinin followed, within a week or ten days, by a rise, sometimes to enormous heights. The strength of the patient's reaction to the incompatible transfusion varies from being so weak as to pass unobserved to being strong enough to kill.

A male patient aged 54, of blood group B, was inadvertently transfused at a very slow drip rate over a period of 5½ hours with about 460 cm.³ of seven days old stored blood of group A. The transfusion was stopped as soon as it was noticed that the blood was labelled group A. The patient had complained of no symptoms whatever, and there had been no rise of temperature or pulse rate. Six hours later the pulse rose to 102 and the temperature to 100° F. [about 38° C.] but the patient still felt well. Within 12 hours the temperature was normal and remained normal or sub-normal. In 24 hours the pulse dropped to 76. He had occasional pyrexia before the transfusion. No serious complications developed and the patient's condition remained satisfactory. He was observed for several months.

Examination of blood taken from the patient on the day before the incompatible transfusion and of the conserved erythrocytes of the donor confirmed that the recipient was group B and the donor group A. The anti-A titre of the patient's serum was 100. On the third day after the transfusion it was 16, and thereafter rose rapidly and attained a peak of 25,600 on the fifteenth day. The titre fell slowly, and eight months later was not quite back to its pre-transfusion level. In the blood taken on the third day, agglutinates of 20 to 30 erythrocytes were seen lying free among large numbers of unagglutinated cells; on the fourth day there were a few small agglutinates but none on the fifth day.

In an attempt to find an *in vitro* explanation for the absence of symptoms, the sera of the donor and recipient were tested for agglutinin strength and their erythrocytes for sensitivity to iso-agglutination. These tests were made eight months after the incompatible transfusion when the strength of the recipient's anti-A agglutinin was approximately what it had been just before the transfusion. The group A donor's serum did not contain very powerful anti-B, and the author suggests that this agglutinin in no way harmed the recipient's cells and that absence of symptoms may in part be attributed to this. The recipient's anti-A agglutinin was of just less than average strength, whilst both donor and recipient

erythrocytes were of average sensitivity. The agglutinogens A and B are not confined to erythrocytes, but occur also in the plasma. Thus the plasma of a group A person contains A agglutinin. *In vitro* tests provided no evidence that the recipient's plasma protected its erythrocytes from the donor's iso-agglutinins and vice versa.

The author concludes that the *in vitro* tests did not fully explain the absence of symptoms and suggests the absence may have been due to the incompatible blood being given at a very slow drip rate.

437

ON THE INHERITANCE AND LINKAGE RELATIONS OF ACHOLURIC JAUNDICE

by R. R. Race, *Annals of Eugenics*, 11, 365-384, December 1942

This paper reports a search for linkage between the gene for acholuric jaundice and the common "physiological" genes, carried out at the Galton Laboratory, University College, London and the British Postgraduate Medical School, Hammersmith.

Nearly 200 members of 26 families were examined hæmatologically for the signs of acholuric jaundice by Dr. Janet Vaughan and Miss Olive Booth. They were also tested for the A₁A₂ BO and MN blood groups and for the ability to secrete the ABO antigens in the saliva, and to taste phenylthiocarbamide. Eye colour and freeness or attachment of the ear lobes were also scored, although the manner of inheritance of these characters is not on the sure basis of those mentioned before.

The war brought the investigation to an end, but not before evidence had been collected against partial sex-linkage and against close autosomal linkage with any of the genes responsible for the A₁A₂BO blood groups, the MN blood groups, secretion of the ABO antigens in the saliva, eye colour and attachment of ear lobes. The figures for taste-testing were inconclusive.

A year or so after the close of the investigation the Rh groups were discovered. This indicates what a laborious undertaking the great work of mapping the human chromosomes will be.

438

THE GROUP-SPECIFIC SUBSTANCES, A, B, M, N AND Rh: THEIR OCCURRENCE IN TISSUES AND BODY FLUIDS

by K. E. Boorman & B. E. Dodd, *Journal of Pathology and Bacteriology*, 55, 329-339, July 1943

That the group-specific substances A and B occur not only in erythrocytes but in almost all tissues and body fluids has been known for years. Attempts to demonstrate the erythrocyte agglutinogens M and N in tissues and body fluids were unsuccessful—save that Zacho found them sometimes in malignant tumours—until Kosjakov & Tribulev (1940), by the use of a modified inhibition technique, detected them in non-malignant tissues. As the addition of saliva to anti-Rh sera did not affect the agglutinin, American workers have concluded that the recently discovered Rh antigen is absent from saliva.

The present authors, of the South-West London Blood Supply Depot (*Medical Research Council*), have demonstrated the presence of M, N and Rh group-specific substances in tissues and body fluids. To detect Rh their technique was essentially the same as the inhibition technique which is used to detect A and B; it depends on the reduction in agglutinin strength which takes place when an antiserum is mixed with a substance containing the corresponding antigen. The reduction is measured by comparing the titre of a serum before and after mixture with the antigen. Every attempt to detect M and N by the inhibition technique failed because non-specific absorption was so great: that is, substances which contained only M would absorb not only anti-M specifically, but also anti-N non-specifically and vice versa. When the inhibition technique was modified according to suggestions made by Kosjakov & Tribulev for eliminating error due to non-specific absorption, M and N were disclosed in saliva and in tissues as these workers had described. The modified technique took account of Kosjakov & Tribulev's

finding that M group-specific substance saturated with anti-M serum cannot affect either anti-M or anti-N sera, but saturated with anti-N serum it can still specifically inhibit anti-M serum. Similarly, N substance saturated with anti-N serum can inhibit neither anti-M nor anti-N, but saturated with anti-M it inhibits anti-N.

Boorman & Dodd believe that earlier workers failed to find M and N in tissues because they could not deal with non-specific absorption and because they used extracts rather than suspensions of tissues. M and N seem to be only slightly soluble in water, for very little can be detected in saliva, and alcohol is said to destroy them. So neither aqueous nor alcoholic extracts would be likely to contain M or N. Whilst there are considerable amounts of Rh substance in the tissues, very little can be found in saliva, probably because it is almost insoluble in water.

The authors suggest that the Rh group-specific substances in foetal tissues fail to neutralize maternal anti-Rh and prevent hæmolytic disease of the newborn because the neutralization of agglutinins which cross the placenta from the maternal to the foetal circulation is effected by antigens in the body fluids, and that tissue antigens play little, if any, part. Similarly, in the few cases in which the ABO groups may cause hæmolytic disease and the baby probably belongs to the "non-secretor" class, the maternal agglutinin is not neutralized because the antigen is absent from the body fluids. Hartmann (1938) has shown that while the ABO antigens occur in the tissues of both secretors and non-secretors, and are present in alcohol- and water-soluble forms in secretors, they do not occur in water-soluble form in non-secretors, and are therefore almost completely absent from their body fluids. Boorman & Dodd conclude that if the following two conditions are satisfied hæmolytic disease of the newborn may result: (i) an incompatibility between the maternal serum and the foetal erythrocytes, and (ii) an insufficiency of the corresponding antigen in the body fluids of the foetus.

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Anæmias and their Treatment

439

NUTRITIONAL IRON DEFICIENCY ANÆMIA IN WAR-TIME. I. The Hæmoglobin Levels of 831 Infants and Children

by L. S. P. Davidson, G. M. M. Donaldson, M. J. Dyar, S. T. Lindsay & J. G. McSorley, *British Medical Journal*, 2, 505-507, 31/10/42

In this paper, workers in the Department of Medicine of Edinburgh University report the results of a survey of hæmoglobin levels in 442 infants and pre-school children (318 from birth to 23 months; 124 from 2 to 4 years) and 389 school-children of 5 to 12 years. The Haldane hæmoglobinometer (13.8 g./100 cm.³ equalling 100%) was used throughout the investigation, and all apparatus was checked against a standard set.

Results were compared with those obtained in a similar investigation made a few years before on Aberdeen children of the same age groups (Davidson & Campbell, 1935). Graphic representation of the results in both investigations shows a close parallelism in the curves of hæmoglobin percentages at different ages. From the 4th month there is a gradual fall which becomes more acute from the 8th to the 11th months. There is then a gradual rise, more rapid in the Edinburgh series, until 2 years of age. From 2 to 5 years, there is a progressive rise in hæmoglobin percentage, with higher values in the Aberdeen series. From 5 to 12 years, the rise is continued, with fluctuations, and comparison of the two curves shows that the hæmoglobin level was considerably lower in the Edinburgh series (average difference of 10% for all ages in this group). The Edinburgh children had no obvious signs of malnutrition.

Analysis of the figures in these two and in a third (Wills, Mackay, Bingham & Dobbs, 1942) series showed that none of the Aberdeen (1935) children had a hæmoglobin of less

than 80%, whereas almost half the Wills *et al.* (1942) and more than half of the Edinburgh (1942) children had hæmoglobin concentrations below that level.

The conclusions drawn from this study were that (i) after three years of war there was no significant change in infant hæmoglobin levels; (ii) there was a significant fall among children of school age; (iii) there should be provision of school meals of high iron content, and propaganda to encourage the consumption of iron-rich foods by children of school age.

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¹ Wills, L., Mackay, H. M. M., Bingham, K. & Dobbs, R. H. (1942) *J. Hyg., Camb.* 42, 505
² [see *BMB* 441]

440

NUTRITIONAL IRON DEFICIENCY ANÆMIA IN WAR-TIME. II. The Hæmoglobin Levels of 3,338 Persons from Birth to 55 Years of Age

by L. S. P. Davidson, G. M. M. Donaldson, S. T. Lindsay & J. G. McSorley, *British Medical Journal*, 2, 95-97, 24/7/43

In a previous paper (Davidson, Donaldson, Dyar, Lindsay & McSorley, 1942) investigations on hæmoglobin levels in 442 infants and pre-school children and 389 schoolchildren were reported. Since the publication of this paper, the *National Physical Laboratory* provided correction factors for the Haldane hæmoglobinometer used, which indicated that the reported readings were approximately 2% low. A further 121 infants and pre-school children, 633 schoolchildren, and 1753 adolescent and adult males and females have been examined, making a total for the whole series of 3338 individuals. Of these, 563 were infants and pre-school children (birth to 4 years); 917 municipal primary-school children (5 to 12 years); 105 private-school children (5 to 12 years); 518 adolescent males and females (13 to 19 years); 620 adult males and females (20 to 54 years); 45 multiparous women; 570 pregnant women. All readings were adjusted in accordance with the correction factors.

The standard of normality for the groups, birth to 4 years, was considered as 85% \pm 5% (Haldane); for the groups 5 to 12 years, 12 to 18 years, and for adult females, 95% \pm 5% (Haldane); for adult males 100% \pm 5% (Haldane) and for pregnant women 85% \pm 5% (Haldane). "Clinical anæmia" was considered to be present if the hæmoglobin was below 80% (Haldane) for all groups except the group of pregnant women, where 70% (Haldane) was the arbitrary figure chosen. Using this standard, "clinical anæmia" was found to be present in 39% of municipal primary-school children, approximately 5% of private-school children, 12% of adolescent females, 7% of adult females, 24% of pregnant women, and less than 1% of adolescent and adult males.

The main conclusion (made with some reservations) from this study is that the incidence of "clinical anæmia" in Edinburgh municipal school children is significantly higher than it was in comparative Aberdeen children a few years before the war (Davidson & Campbell, 1935). Standards of normality and errors of estimation are discussed.

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² [see *BMB* 439]

441

ANÆMIA IN WOMEN AND CHILDREN ON WAR-TIME DIETS

by L. Wills, H. M. M. Mackay, K. Bingham & R. H. Dobbs, *Journal of Hygiene*, 42, 505-526, October 1942

The investigation reported in this paper was undertaken to determine whether (i) anæmia was prevalent among women and children; (ii) there was any evidence of increased incidence of anæmia; (iii) there was any evidence as to the ætiology of the anæmia. Preliminary details of the investigation had previously been published (Mackay, Wills, Dobbs & Bingham, 1942). Haldane's hæmoglobinometer (13.8 g./100 cm.³

equalling 100%) was used throughout the investigation. The estimations were made on 544 women (nurses and medical students; factory workers; housewives) and 530 children (364 aged 6 months to 5 years; 90 aged 5-13 years; 38 aged 13-15 years; 38 adolescent factory workers aged 14-18 years).

The mean haemoglobin value of the women was 89.5% (ranging from 56%-120%), similar to the mean obtained by Davidson & Fullerton (1938) in 1937 for a group of poor nulliparous women. These figures are significantly lower than those obtained in other series by Price-Jones (1931) and Jenkins & Don (1933).

There was a significant difference in the haemoglobin values for nurses and students working in London (90.6%) and in country (84.1%) hospitals. Mean values for the two different occupational groups (nurses and students) working at the same hospitals approximated closely. Mode of life and working conditions did not differ materially in the London and rural hospitals, but there were differences in the diet. The estimated daily iron intake of the London group was 10.8 mg. and that of the rural group 9.2 mg. The 159 workers at a factory in a small town near London had a higher (94.0%) mean haemoglobin level than the London housewives (89.6%).

Of the children, the average haemoglobin level at 6-12 months was 75.4%, dropping to 72.8% between 1-2 years, and gradually rising again to 81.8% between 4-5 years of age. In 90 children of the 5-13 year age-group, the mean haemoglobin level was 80.3%; in the 13-15 year group it was 89.3% and in the 14-18 year group of working girls it was 98.7%.

In all the groups of women and children, except the small group of factory girls, mean haemoglobin values were significantly lower than in previous comparable groups, and the authors believe these reductions to be the expression of a nutritional anaemia. They believe that iron deficiency is one important aetiological factor, but that other dietetic deficiencies are implicated, and that in nurseries a high incidence of infection has increased the incidence and severity of an anaemia primarily due to iron deficiency.

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442

DISCUSSION ON NUTRITIONAL ANAEMIA IN CHILDREN AND WOMEN: A War-time Problem

by H. M. M. Mackay, L. Wills, R. H. Dobbs, K. Bingham, L. Findlay, H. M. Sinclair, L. S. P. Davidson, J. Yudkin & T. S. Marshall, *Proceedings of the Royal Society of Medicine*, 36, 69-84, December 1942

In the paper (Mackay, Wills, Dobbs & Bingham) which opened this discussion attention was drawn to previous observations (McCance, Widdowson & Verdon Roe, 1938; Ross & Summerfeldt, 1936; Spence, 1934) on the influence of economic status on mean haemoglobin level and on the relationship between infantile anaemia and anaemia of the mother during gestation (Strauss, 1933; Mackay, 1933, 1935). There was evidence of a higher morbidity rate in babies with moderate anaemia (Mackay & Goodfellow, 1931). After a reference to fallacies due to obtaining samples of blood for haemoglobin estimation from the ears of young children, comparisons are made between the results of different haemoglobin surveys undertaken in Britain. Curves of mean haemoglobin levels in groups of working-class children under 5 examined before the war by different British investigators (Davidson, Fullerton & Campbell, 1935; Fullerton, 1937; Hutchison, 1938) show close agreement and correspond also to the later war-time series of Wills, Mackay, Bingham & Dobbs (1942). There was also a close similarity between the war-time mean levels of Wills *et al.* for children in or near London and those of Davidson, Donaldson, Dyar, Lindsay & McSorley (1942) for Edinburgh. Haemoglobin levels of women were significantly lower than those of comparable groups before the war.

From examination of evidence discussed in this paper it appears probable that there has been a reduction of haemoglobin levels in some social groups, and it is possible, although not demonstrated, that there has been a rise in other groups as a result of increased employment, rationing and food "priorities."

The authors conclude by recommending that infants should be given iron supplements and that, for older groups, iron should be added to bread.

Another speaker, Dr. L. Findlay, in discussing the blood as an index of health, referred to the results of a survey (Findlay, 1937) undertaken on children admitted to a London hospital in a poor district. These haemoglobin estimations were made from ear-punctures, and results may have been too high, but a subsequent unpublished series made from finger- and heel-punctures showed no evidence of a serious incidence of anaemia. Later observations made in war-time on children admitted to the *Radcliffe Infirmary* from Oxford and its environs revealed a high proportion of subnormal haemoglobin and erythrocyte levels, although the general condition of the Oxford children appeared to be superior to that of the London children. The author discusses these and other relevant findings and concludes that the haemoglobin level is not a true index of the health of the child, nor necessarily of the iron content of the diet; that it varies with age, sex, and other factors; and that the term "nutritional anaemia" is too loosely employed.

Dr. H. M. Sinclair referred to observations made in the course of the Oxford Nutrition Survey which showed an increase in anaemia. If this were due to iron deficiency, a simple remedy would be the use of iron instead of aluminium cooking pots. A potato boiled in an iron vessel contains about twice as much iron as one cooked in an aluminium vessel. With apples boiled for only 5 minutes, the iron content is nearly a hundred times greater if an iron vessel is used. Another simple measure is the provision of ferrated bread. In the author's view, there was no danger of toxic effects from excessive intake of iron.

Dr. R. H. Dobbs discussed anaemia in young women, with reference to the results reported by Wills *et al.* (1942), and sources of error in haemoglobinometry. It was particularly important to obtain freely flowing blood from a warm limb.

Professor L. S. P. Davidson summarised results of a haemoglobin survey which has been reported elsewhere (Davidson *et al.*, 1942).

Dr. J. Yudkin had recently examined 300 mothers and children in Scotland and had found a decrease in haemoglobin levels as compared with previously published figures, although this was not so great as that found by Professor Davidson. It was important that all workers on this problem should maintain close contact and compare methods and results.

Dr. T. S. Marshall reported results of estimations on male and female blood donors. The mean haemoglobin level (Haldane-Gowers haemoglobinometer, standardised by National Physical Laboratory) was 100% in 100 males; 84% in 65 post-menopausal women; 82% in 220 women in the reproductive period of life. Differences as great as 12-18% were observed in the same subjects (a) immediately on arrival, after cycling or hurrying, (b) after 20 minutes recumbency. This suggested a possible reason for the high levels reported by Wills *et al.* (1942) in factory girls.

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¹ [see BMB 439]

² [see BME 441]

TREATMENT OF ANÆMIA IN SCHOOL-CHILDREN WITH IRON AND ASCORBIC ACID

by L. S. P. Davidson & G. M. M. Donaldson, *British Medical Journal*, 1, 76-77, 15/1/44

In the first school, the children in both the control and the experimental groups were unselected, but were divided into three groups. Group A consisted of children who went home for a midday meal; Group B included those who took school dinners, for which they paid; while Group C included those children who had free school dinners. The children in the experimental groups were given 3 grains [about 200 mg.] of ferrous sulphate in tablet form daily for 5 days in each week. Hæmoglobin estimations were made at the outset of the experiment and again after 3 months of treatment.

In the control groups there was no significant rise in the mean hæmoglobin levels at the second examination. In experimental Groups B and C, the rise in the hæmoglobin levels was significant but in Group A, although there was a rise, it was not statistically significant. An analysis of the hæmoglobin figures of those children whose initial hæmoglobin level was less than 80 % showed that of 59 such children in the control series, 31 (52.5 %) still had hæmoglobin figures of less than 80 % at the second examination; while of 71 receiving iron therapy, only 24 (33.8 %) still had hæmoglobin figures of less than 80 % at the second examination. This improvement in the treated group is statistically significant.

In the second school there were 57 unselected children in the control group, 56 unselected children in experimental Group A who were treated with 25 mg. of ascorbic acid daily for 5 days a week, and 57 unselected children in Group B who were given 25 mg. of ascorbic acid daily and 3 grains of ferrous sulphate daily for 5 days a week. In the control group and in Group A there was no significant rise in the hæmoglobin values when the estimations were repeated at the end of 3 months. In Group B the rise in hæmoglobin level was significant.

In the third school, 54 children whose original hæmoglobin level was 80 % or less were divided in two equal groups, the experimental group being given 25 mg. of ascorbic acid daily and 6 grains of ferrous sulphate daily for 5 days a week over 6 months. Both control and experimental groups showed an increase in hæmoglobin but the mean levels in the treated group were significantly greater than those found in the control group. These results show that the hypochromic anæmia of these children was mainly conditioned by an insufficiency of iron in the diet and that supplement of 25 mg. of ascorbic acid daily had no effect in raising the hæmoglobin levels.

144

TREATMENT OF PERNICIOUS ANÆMIA WITH AN EXPERIMENTAL PROTEOLYSED LIVER PREPARATION: Preliminary Observations

by L. J. Davis, L. S. P. Davidson, D. Riding & G. E. Shaw, *British Medical Journal*, 1, 655-656, 29/5/43

The superiority of whole liver over parenteral injections of liver extracts in the treatment of certain types of macrocytic anæmia, such as those occurring in pregnancy, sprue and tropical nutritional deficiency states is well known. Among the disadvantages of whole liver are its relatively high cost, the difficulty of ensuring a regular supply, the distaste caused by its prolonged administration, and the uncertainties attending its assimilation in patients whose digestive and absorptive processes are impaired. Accordingly it was considered that it might be an advantage to administer to such patients whole liver in a soluble predigested form. Papain was chosen as a suitable enzyme for predigestion of the liver and the following method of preparation was used:

Take 330 pounds [about 150 kg.] of minced liver in a steam-heated pan. Add 36 gallons [about 160 l.] of water and 660 g. of papain, and heat the mixture to 60° C. Maintain the temperature at this level for three hours. Then raise the temperature to 100° C. and boil vigorously for ten minutes. Strain the hot digestion mixture through cloth, and concentrate the filtrate at a low temperature in a vacuum still to 20 gallons. Clarify the concentrate by filtration, using sterilized kieselguhr as a filter aid, and then sterilize by filtration through suitable asbestos pads. Dry the sterile liquid in a low-temperature vacuum oven. The product thus

obtained is a dry, sterile, granular light-brown powder which is slightly hygroscopic. It is completely soluble in hot or cold water, giving a solution that is reasonably palatable and free from the characteristic liver flavour. Riboflavin is present in a concentration of 10 mg. per 100 g.

Five typical cases of pernicious anæmia were used to test this product. Without exception a satisfactory response was noted within a few days of the institution of treatment. The average rise in erythrocytes per mm.³ was 0.94 million during the first two weeks and 1.74 million during the first three weeks of treatment. An adequate daily dose appeared to be 2 drachms [about 4 g.], but in certain resistant cases it is possible that a larger amount may be desirable. This amount is derived from less than two ounces [about 60 g.] of raw liver.

[This proteolysed liver preparation is now commercially available under the trade name "Hepamino."]

445

SENSITIVITY TO LIVER EXTRACT

by J. G. McSorley & L. S. P. Davidson, *British Medical Journal*, 1, 714-716, 27/5/44

A search of the literature since Schlesinger (1930) first reported reactions to liver extract has revealed less than a hundred cases. Reactions may be classified as: (i) primary, which occur after the first injection, and have become rare with the increasing purity of liver preparations and adoption of routes of administration other than intravenous; (ii) secondary, which occur after varying periods of oral, intravenous or intramuscular liver therapy and are undoubtedly of an allergic character.

The literature contains reports of sensitivity to all brands of liver extract. Some patients who have reacted to one brand do not react to another. However, such patients tend to become sensitized also to alternative brands, and the experience of the authors indicates that sensitivity usually extends to all liver extracts in patients who have had marked reactions to one preparation. Reactions usually increase in severity with successive injections. The commonest are: flushing, tachycardia, erythema, and localized urticaria. In severe cases, there may be generalized urticaria, bronchospasm, vomiting, rigor, hyperpyrexia, collapse, anaphylactic shock and other allergic manifestations.

The authors found skin tests to be of some value in assessing sensitivity, although they agree that their value is limited. Their technique is to inject intradermally 0.05 cm.³ of undiluted liver extract into the volar surface of the forearm, with a control injection of saline at the same level. A wheal of 15 mm. or more in diameter developing in 15-30 minutes is accepted as a positive reaction. As there may be severe general reactions to this test dose, adrenaline should be available.

With regard to treatment, patients were arbitrarily divided into those with (i) mild symptoms and (ii) severe constitutional reactions. In mild cases 3 minims [about 0.174 cm.³] of 0.1 % adrenaline hydrochloride were injected concurrently with the liver preparation and in some cases no further treatment was required. In other cases the quantity of liver extract injected was reduced to $\frac{1}{2}$ or $\frac{1}{4}$ of the dose which produced a reaction and the periods between injections were correspondingly reduced. Other measures have been recommended by various writers but proof of their value is lacking. It has been claimed (Barfred, 1942) that butyl alcohol removes a considerable part of the factor in liver extract responsible for allergic reactions, but the present authors found that material so treated produced reactions in 2 sensitive patients.

In severe cases oral ingestion of liver or hog-stomach preparations should replace parenteral liver therapy, or desensitization should be carried out. A technique of desensitization which was found satisfactory in 17 severe cases is described. The authors prefer desensitization to substitution of oral preparations, as parenteral therapy is cheaper and more effective. Desensitization, however, may be dangerous unless performed by someone experienced in the danger of anaphylactic reactions.

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AUTOLYSED YEAST IN THE TREATMENT OF NUTRITIONAL MACROCYTIC ANÆMIA

by G. R. Sippe, *British Medical Journal*, 1, 656-658, 13/5/44

Nutritional macrocytic anæmia has been reported from India, China, Africa, and Macedonia, and has been attributed to the lack of one or more essential factors in the diet. In this paper from the Bacteriological Laboratory of Reduit, Mauritius, the author states that the condition is also common in Mauritius among those who refrain on religious grounds from eating beef flesh. Wills (1934) showed autolysed yeast to be active in the treatment of this anæmia. The present author reports the results in 6 cases treated by oral administration of a waste product of the manufacture of alcohol by fermentation of molasses. Its potency was attributed to the presence of autolysed yeast. The product was obtained as a thick fluid from the bottom of the fermentation vats. Before use, it was passed through a coarse filter and heated at 70° C. for one hour. The quantity of the product used in treatment was 3-6 ounces (about 90-180 cm.³) daily. Results of the analysis of samples are tabulated.

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447

HÆMOLYTIC ANÆMIAS

by L. J. Davis, *Edinburgh Medical Journal*, 50, 589-616, October 1943

This is the text of a Honeyman Gillespie Lecture, in which there is a brief consideration of fundamental principles of erythrocyte destruction and regeneration, followed by a survey of the different types of hæmolytic anæmia in the light of recent views and observations. The author adopts a provisional classification of the hæmolytic disorders according to their known or supposed ætiology:

- i. *Abnormality of the erythrocytes*
 - Familial acholuric jaundice
 - Sickle-cell anæmia
 - Nocturnal hæmoglobinuria
- ii. *Hæmolysins*
 - Transfusion incompatibility
 - Erythroblastosis foetalis
 - Paroxysmal hæmoglobinuria
 - Severe burns
 - Bacterial infections
 - Snake bite
- iii. *Parasitic infection of erythrocytes*
 - Malaria
 - Oroya fever
- iv. *Poisons*
 - e.g. lead, phenylhydrazine, saponin
- v. *Hypersensitivity to drugs or other agents*
 - Sulphonamide anæmia
 - Fabism
 - Baghdad Spring anæmia
- vi. *Cause unknown, but associated with known predisposing factors*
 - Blackwater fever (sub-tertian malaria)
 - "Symptomatic" hæmolytic anæmias (Hodgkin's disease; reticuloses; carcinoma, etc.)
 - March hæmoglobinuria (postural defect)
- vii. *Cause completely unknown*
 - Acute hæmolytic anæmia (so-called "Lederer's anæmia")
 - Miscellaneous subacute and chronic hæmolytic anæmias
 - Cooley's (Mediterranean) anæmia

Each group of hæmolytic disorders is discussed under the above headings, and 108 references to the literature are given.

448

SYMPTOMATIC HÆMOLYTIC ANÆMIA: A REPORT OF FOUR CASES

by L. J. Davis, *Edinburgh Medical Journal*, 51, 70-83, February 1944

The term symptomatic hæmolytic anæmia was introduced by Dameshek & Schwartz (1940) to embrace cases of acquired

hæmolytic anæmia displaying an apparent ætiological relationship to certain morbid processes such as carcinomatosis, leukæmia, Hodgkin's disease, sarcoidosis, hepatitis, teratoma of the ovary, and various infective conditions such as tuberculosis and lobar pneumonia. Dr. Davis reports in detail 4 further cases in which the primary diseases were adenocarcinoma of the pancreas, reticulosis, Hodgkin's disease and acute myeloid leukæmia. The author stresses the need for exclusion of other types of hæmolytic anæmia before this diagnosis is accepted. Microspherocytosis and increased erythrocyte fragility may or may not occur. These were absent in the present cases, all of which were macrocytic to a greater or less extent.

The mechanism of hæmolysis is obscure. In cases where the marrow is extremely affected it is possible to postulate a disturbance of marrow function resulting in the production of abnormal erythrocytes having impaired survival values. The author suggests that the neoplastic process may exert an abnormal stimulus to increased activity of the reticulo-endothelial cells, and points to the infrequency with which the spleen becomes the site of carcinomatous metastases because of the ability of the numerous reticulo-endothelial cells of this organ to destroy wandering tumour cells. Thus it is conceivable that the constant exercise of such a destructive mechanism directed against tumour cells may result incidentally in an increased destruction of erythrocytes. However, this mechanism would not account for all cases. The prognosis and treatment necessarily depend upon the underlying conditions. All the 4 cases described died, but a few cases in the literature benefited by the removal of the original tumour and by splenectomy.

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449

ACUTE HÆMOLYTIC ANÆMIA: REPORT OF A CASE PRESENTING HITHERTO UNREPORTED FEATURES

by J. P. Currie, *British Medical Journal*, 2, 8-10, 1/7/44

This paper from the Royal Infirmary, Glasgow, gives a brief summary of the growth of knowledge of acute hæmolytic anæmia and reports a case of this rare condition showing auto-agglutination and auto-hæmolysis at room temperature. The reader is referred to the full review of the subject by Dameshek & Schwartz (1940).

Hayem (1898) and Minkowski (1900) first recognised hæmolytic jaundice as an entity apart from liver or bile-duct disease. Chauffard (1907) showed that in chronic hereditary acholuric icterus with splenomegaly the erythrocytes were abnormally fragile in hypotonic solution, and other workers described "acquired hæmolytic icterus," a type of acholuric jaundice which was not hereditary and occurred alone or in the course of other diseases. In a third type, "hæmolysin icterus," the serum, at the height of the disease, contained an isohæmolysin. Each of the three types was subdivided into acute, subacute and chronic. Roth (1912) found an auto-agglutinin and an auto-hæmolysin in a case, but said that "hæmolysin" was an unjustifiable term and that the hæmolysis was due to an abnormality of the erythrocytes. The existence of an acquired type was gravely doubted. In 1925 Lederer "discovered" the "new" disease, acute hæmolytic anæmia, although similar cases had been reported previously. He did not mention isohæmolysins or auto-agglutinins.

It is very difficult to trace cases because they may be given a variety of names, e.g. "atypical anæmia," "atypical pernicious anæmia," "acute pernicious anæmia," etc.

Whilst many hæmolytic anæmias are due to bacteria, protozoa and chemicals, no cause is known for the majority of cases. There are two main views:

(i) that the serum or tissues contain an auto-hæmolysin for the patient's own erythrocytes.

(ii) that lysis is caused by normal wear of abnormally fragile erythrocytes.

That the marrow responds so well suggests it is not injured and favours the first view.

Donath & Landsteiner (1905) showed that the lysis in paroxysmal hæmoglobinuria is caused by isohæmolysins and they have been found in several cases of acute hæmolytic anæmia, but with regard to the ætiology of the disease the

finding of auto-hæmolysins is of greater significance; these have rarely been demonstrable and only under abnormal conditions, e.g. at ice-box temperature. Early workers noted auto-agglutination in acute acquired hæmolytic jaundice, and said its occurrence was constant and of diagnostic value. This observation was for long overlooked and only recently re-made.

Dameshek and Schwartz made a hæmolysin against guinea-pig erythrocytes by injecting them into a rabbit, and then, by injecting varying amounts of the rabbit serum into guinea-pigs, were able to produce various types of hæmolytic syndrome—from subacute hæmolytic anæmia with small doses, to fulminating hæmolytic anæmia and hæmoglobinuria with large doses of the hæmolysin. The clinical conditions, spherocytosis, increased erythrocyte fragility, reticulocytosis, pseudo-macrocytosis, etc., could be produced in the same way, and it is inferred that the clinical syndromes are due to the amount of hæmolysin present.

The author describes the case of a man of 37 who became suddenly ill with acute hæmolytic anæmia, with lemon-yellow skin and mucous membranes, striking pallor, tender palpable spleen, and hæmoglobinuria. There was no bilirubinuria.

Blood-grouping preparatory to transfusion was made difficult by the patient's serum agglutinating his own erythrocytes at room temperature. By performing the tests at body temperature the patient's group was shown to be O. In addition to the normally occurring isoagglutinins anti-A and anti-B, the patient's serum contained an agglutinin which at room temperature—not at body temperature—agglutinated his own corpuscles but not those of normal group O persons—it was literally an auto-agglutinin. [Usually "auto-agglutinin" is used for the commonest type of cold agglutinin which agglutinates not only the corpuscles of its donor but those of any other person.] Heating to 60° C. did not destroy the antibody and the addition of complement caused hæmolysis. [By saying "The associated hæmolysin requires the presence of complement" the author suggests that the agglutinin and the hæmolysin are not the same antibody. Hæmagglutination and hæmolysis are closely related and it is widely believed that the addition of complement causes the agglutinin to lyse the erythrocytes.] Standing normal group O cells in the filtrate from the patient's crushed, washed erythrocytes made them sensitive to the auto-agglutinin—it was impossible to determine whether the corpuscles, suspended in a hæmoglobiniferous fluid, were also lysed. After blood transfusion recovery took place, the auto-agglutination and auto-hæmolysis disappeared, and serum obtained whilst he was ill did not affect his corpuscles after recovery, but these corpuscles treated with the filtrate mentioned above were rendered agglutinable. After recovery the serum still contained the auto-agglutinin—it agglutinated cells obtained whilst he was ill. Recovery caused an alteration in the erythrocytes, not in the serum. It is concluded that there were: (a) an auto-agglutinin, an auto-agglutigen and an auto-hæmolysin; and it is suggested there was also (b) an auto-hæmolysinogen.

Only one pint [about 570 cm.³] of citrated group O blood was given on the sixth day of the illness, but the author does not regard it as a case of dramatic recovery due to a single transfusion—the disease had limited itself by the time the blood was given. Several transfusions may be needed and in some cases they may be useless. Splenectomy may cure some, and it is thought that the hæmolysin is made in the spleen.

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erythrocytes in different types of anæmia. Results were examined by construction of graphs showing the relation of the number of surviving donor cells to the days after transfusion. In the simple types, such as idiopathic hypochromic anæmia (6 cases), only a linear type of decay was found, but in hæmolytic anæmia (3 cases) the plotted results showed considerable curvature and the average life of the cell was much reduced. The method therefore allows a quantitative analysis of the amount of pathological hæmolysis in other anæmias. To facilitate numerical description of the results, a general equation connecting the number of surviving cells with the interval since transfusion was developed. Seven cases of anæmia complicating infections of varying severity were transfused, some on several occasions. These cases showed different rates of hæmolysis, and the average life of the transfused cells ranged from 8.4 to 56.3 days. The shape of the decay curves varied from a curvature as great as that seen in clinical hæmolytic anæmia, to a straight line such as had been found in the cases of idiopathic hypochromic anæmia. The cases which were judged more severe on clinical grounds showed more rapid hæmolysis and in the cases where the average life was shortest there was increased reticulocytosis and bilirubinæmia. Thus the anæmia which complicates acute infection is apparently due to unduly rapid erythrocyte destruction, but in chronic infections the destruction rate is normal. Abnormally rapid hæmolysis was also found in cases of puerperal pernicious anæmia, leuco-erythroblastic anæmia and myelomatosis, while in cases of thyrotoxicosis, chronic nephritis and pernicious anæmia under treatment with liver (1 case of each), erythrocyte destruction occurred at the normal rate.

In a discussion of their results, the authors relate the mathematical expression of their data to the hypothesis recently developed by Macgrath, Martin & Findlay (1943) that a (species-specific) lytic enzyme and an inhibitor are concerned in the mechanism of hæmolysis.

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¹ [see *BMB* 87]

451

STUDIES IN THE ANÆMIAS OF INFANCY AND EARLY CHILDHOOD. XII.—THE REGENERATION RATE OF HÆMOGLOBIN AND THE LIFE SPAN OF ERYTHROCYTES IN NORMAL AND PATHOLOGICAL CONDITIONS

by H. S. Baar & T. W. Lloyd, *Archives of Disease in Childhood*, 18, 1-21, March 1943

Blood containing varying numbers of reticulocytes was incubated in sterile citrated balanced salt solutions, with or without added glucose or serum, and the rates of maturation of the reticulocytes were observed by hourly counts. The curve of maturation shows a decreasing velocity of disappearance of the reticulocytes. The authors consider that this is due to the initiation of necrobiotic changes in the erythrocyte and does not represent a real decrease of the velocity of maturation. The maturation time is therefore obtained by extrapolation of the initial slope to the ordinate zero. The average maturation time of normal reticulocytes by this method is about seven hours. The maturation time in cases with reticulocytosis is usually longer, but there is no fixed relation between either the number of reticulocytes or the amount of reticular substance and the maturation time. The only condition in which a maturation time shorter than the normal was found is untreated pernicious anæmia.

The daily regeneration rate is obtained by multiplying the number of reticulocytes per cent. by twenty-four and dividing by the maturation time in hours. One hundred divided by this figure gives the life span of erythrocytes in days if the number of erythrocytes is constant. From an average reticulocyte count of 0.7% and a maturation time of seven hours, an average life span of forty-two days has been deduced. The regeneration rate of hæmoglobin is identical with that of erythrocytes as long as the colour index remains unchanged.

450

THE DESTRUCTION OF TRANSFUSED ERYTHROCYTES IN ANÆMIA

by G. M. Brown, O. C. Hayward, E. O. Powell & L. J. Witts, *Journal of Pathology and Bacteriology*, 56, 81-94, January 1944

The authors applied the Ashby technique of differential agglutination to the study of the survival of transfused

STUDIES IN THE ANÆMIAS OF INFANCY AND EARLY CHILDHOOD. XIII—EXPERIMENTS ON BLOOD REGENERATION AND THEIR SIGNIFICANCE FOR THE LIFE SPAN OF ERYTHROCYTES

by H. S. Baar, *Archives of Disease in Childhood*, 18, 65–87, June 1943

A curve representing the rise of hæmoglobin or of erythrocytes does not indicate the real regeneration but is the result of two factors—the formation (or, more exactly, the release from the bone-marrow) of erythrocytes and their destruction. It was decided to separate these two factors in experimental anæmia, calculating the real regeneration or the daily hæmoglobin intake from the number of reticulocytes and their maturation time determined *in vitro*, and sometimes *in vivo*, and estimating the destruction, subtracting the observed rise of hæmoglobin from the intake determined in this way. Anæmia was produced by subcutaneous injections of phenylhydrazine hydrochloride in rabbits and guinea-pigs. The daily regeneration of hæmoglobin (= intake) per 100 cm.³ of blood was noted for two- or three-day periods, over some weeks. This figure is calculated by taking the arithmetic mean of two subsequent reticulocyte counts (as a percentage), dividing by 100 and multiplying by 24 over the maturation time in hours. The maturation was determined during the period of high reticulocyte counts for rabbits both *in vitro* and *in vivo*, for guinea-pigs *in vitro* only. These figures, which were 10 hours for rabbits and 8 hours for guinea-pigs, were used for the whole experimental period. The regeneration per 100 cm.³ blood is therefore given by the formula

$$\frac{\text{Hb} \times \text{R}}{100} \times 2.4 \text{ for rabbits and } \frac{\text{Hb} \times \text{R}}{100} \times 3 \text{ for guinea-pigs,}$$

where Hb is hæmoglobin in grams per 100 cm.³ and R the reticulocyte count per cent. of erythrocytes. If this figure be multiplied by the blood volume in decilitres the total daily intake of hæmoglobin is obtained. The actual rise or fall of hæmoglobin in grams per 100 cm.³ in the corresponding period was also observed. If the drop be added and the rise subtracted from the regeneration figure the destruction of hæmoglobin in grams per 100 cm.³ blood is obtained. Summation curves were then constructed for the hæmoglobin regeneration. The shape of the curves is characteristic and indicates that the "master reaction" determining the blood regeneration and hæmoglobin intake under these experimental conditions is an autocatalyzed reversible reaction, and is therefore exclusively determined by the process of the multiplication of nucleated cells in the bone-marrow. In the course of blood disorders, periods of increasing and decreasing bone-marrow activity alternate with periods of equilibrium. The word equilibrium is used here to indicate a state of bone-marrow activity resulting in the output of a constant mass of erythrocytes each day without necessarily any relation to the rate of peripheral erythrocyte destruction, and may therefore be associated with a constant erythrocyte level, with a fall, or with a rise. The only characteristic of such a state is the constant reticulocyte concentration: the points for $\sum \frac{\text{Hb} \times \text{R}}{100} \times k$ fall therefore on a straight line.

From these data it was found that the time of repair is not identical with the duration of life of erythrocytes. It does not represent the regeneration time, but is the result of considerably increased regeneration and less considerably increased destruction. A decrease in the rate of destruction of erythrocytes occurs only in the later stages of repair and only for short periods of time. The majority of erythrocytes formed at one time die at the same time; some may be destroyed without regard to their age, but old age is the main factor which determines the life span of erythrocytes.

hæmolytic anæmias or anæmias which are secondary to other morbid processes, such as malignant neoplasms, leukæmias, metabolic disturbances and infections.

For the diagnosis and prognosis of these anæmias examination of the bone-marrow is essential. The following is the technique used by the authors:

About 1 cm.³ of marrow juice is aspirated from the medullary cavity of the sternum in the usual way, using a "Salah" type needle and a 10 cm.³ record syringe, and is immediately expelled into a watch-glass. After a few seconds the fluid is poured into a second watch-glass. Visible flecks of marrow tissue remain adherent to the first watch-glass; these are picked up with a fine pointed forceps and placed on microscope slides. With the aid of a spreader, the flecks are squashed and with a rapid sliding movement films are made. The degree of pressure exerted is regulated so that the marrow is squashed as lightly as consistent with the production of a satisfactory film. The number and size of the marrow particles varies considerably in different cases. In pernicious anæmia the flecks are large and abundant, while in certain types of aplastic anæmia no visible particles may be present, the appearance of the aspirated fluid differing from peripheral blood only by the presence of droplets of oily fluid. In this latter type of case films are made directly from the fluid. The films are dried in air as quickly as possible and stained by the May-Grünwald or Leishman methods. The erythrocyte precursors are divided into four types:

The Type I erythroblast is a large cell with a deep basophilic cytoplasm and a finely reticulated nucleus. Nucleoli may or may not be present. Included in this cell type are the pro-erythroblast as well as the primitive megaloblast of certain authors. Maturation of the cells, indicated by reduction in size, progressive hæmoglobinisation, and by condensation of nuclear chromatin, progresses through Types II and III to Type IV, the mature normoblast, which is often fully hæmoglobinised and with a dense pyknotic nucleus. The bone-marrow in the relapse stage of pernicious anæmia shows large numbers of Type I and II cells. In iron-deficiency anæmias Types III and IV preponderate. In marrow films from normal individuals, erythroblasts usually constitute about 25 % of all marrow cells.

A marrow smear displaying normoblastic erythropoiesis is one in which the vast majority of the erythrocyte precursors have compact condensed nuclear chromatin, while the recognition of megaloblastic erythropoiesis is based upon the presence of a greatly increased frequency of the primitive basophil erythroblasts (Type I cells), with numerous Type II cells also.

The following is the classification finally adopted, together with the numbers of cases studied in each group:

- I. *With hypocellular, normoblastic marrow*
 - (a) Secondary to exposure to toxic substances: 4 cases
 - (b) Idiopathic, of unknown origin
 - (i) Progressive hypoplastic anæmia with fatal termination: 9 cases
 - (ii) Chronic hypoplastic anæmia, patients surviving two or more years: 2 cases
 - (iii) Relapsing hypoplastic anæmia: 1 case
- II. *With hypercellular, megaloblastic marrow*
 - (a) Occurring in pregnancy and puerperium: 10 cases
 - (b) Idiopathic: 6 cases
- III. *With cellular, normoblastic marrow and arrested myelocyte maturation: 2 cases*

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STUDIES IN REFRACTORY ANÆMIA. I. The Technique and Interpretation of Sternal Puncture Biopsies. Classification by L. S. P. Davidson, L. J. Davis & J. Innes, *Edinburgh Medical Journal*, 50, 226–236, April 1943

The term "refractory anæmia" was first used by Bomford & Rhoads (1941) to embrace the heterogeneous group of anæmias which are refractory, temporarily or permanently, to treatment with any known hæmatinic. It includes anæmias of unknown origin and those resulting from exposure to hæmatotoxic substances, but does not include the

STUDIES IN REFRACTORY ANÆMIA. II. Anæmias with Hypocellular, Normoblastic Marrows by L. S. P. Davidson, L. J. Davis & J. Innes, *Edinburgh Medical Journal*, 50, 355–377, June 1943

Of the 16 cases of refractory anæmias with hypocellular normoblastic marrows described, 4 were secondary to exposure to toxic substances: one had been injected therapeutically with arsenic compounds and a second with gold;

a third had been exposed occupationally to the fumes of benzol and a fourth to trinitrotoluene. The first two recovered after several months, while the third and fourth pairs died in six months and one month respectively. All had intensive treatment with iron, liver and repeated blood transfusions. The 12 remaining cases in this group were of unknown origin.

The average age at which symptoms of anæmia were first noted in this idiopathic group was high, namely 61 years. In all the cases the anæmia was macrocytic or normocytic in character. In only 2 cases were anisocytosis, poikilocytosis, ovality of outline, and macrocytosis sufficiently marked to suggest classical pernicious anæmia in relapse. In the remaining cases the films were less characteristic, although anisocytosis and a variable number of well-filled macrocytes were present, except in 2 cases which presented a normocytic picture. Without exception the hypoplastic process affected all the cells formed in the marrow: erythrocytes, granulocytes and platelets. A reticulocyte count persistently higher than 1% was present in only 3 of the cases, in which counts around 5% were persistently found.

One of the most pertinent questions arising from this study concerns the validity of accepting hypoplastic normoblastic sternal marrow film as pathognomonic of hypoplastic refractory anæmia. The authors consider that when several films made from separate flecks of sternal marrow show a consistent hypocellularity, the chances that the diagnosis of hypoplastic anæmia is correct are increased. The possibility that these findings are fortuitous is rendered still more improbable if they are confirmed by a second sternal puncture at a different site.

Thus the demonstration of a hypocellular, normoblastic sternal marrow picture in a severe anæmia, macrocytic or normocytic in character, with a colour index within or above the normal range, strongly suggests, in the absence of any evidence of a causative factor, that the condition is an anæmia of the type under discussion. If liver therapy has recently been administered, however, a reasonable period should be allowed to elapse for the occurrence of a possible reticulocyte response or a rise in the erythrocyte count before coming to final decision. The reason for this is that, in pernicious and certain other megaloblastic anæmias, the earliest demonstrable response to liver therapy is the conversion of the megaloblastic marrow picture to a normoblastic one. However, this consideration is probably chiefly of theoretical interest, since in the authors' experience the sternal marrow pictures in pernicious and allied anæmias are uniformly hypercellular. The authors cannot find a satisfactory explanation of the mode of production of macrocytes in this type of anæmia, but believe that their presence in conjunction with a hypocellular normoblastic marrow is of diagnostic significance.

Of the 12 patients 9 died, the average period elapsing after the onset of symptoms being seven months. Of the remaining cases, the ultimate outlook for 2 is poor. The other appears to have been keeping in reasonably good health for over two years in spite of a moderately severe anæmia.

455

STUDIES IN REFRACTORY ANÆMIA. III. Refractory Anæmias with Cellular Marrow

by L. S. P. Davidson, L. J. Davis & J. Innes, *Edinburgh Medical Journal*, 50, 431-443, July 1943

Of the 16 cases of refractory anæmia with hypercellular normoblastic marrows, 10 occurred in pregnancy and the puerperium. The authors have fully discussed these cases in a previous paper (1942). To summarize, they were cases of severe anæmia with hæmoglobin readings ranging from 17 to 52% (Haldane), occurring during pregnancy or the puerperium and with megaloblastic sternal marrow pictures. They displayed temporary refractory periods varying from two weeks to four months in spite of intensive parenteral liver therapy supplemented by the administration of iron and vitamin concentrates. In the majority of cases, repeated blood transfusions were necessary for the maintenance of life during the refractory period. Eventually complete recovery occurred in all cases.

The other 6 cases were of idiopathic origin. The average age of this group was 41 years. Four had a histamine-fast achlorhydria, while two had free hydrochloric acid in the

resting gastric juice. The degree of anæmia was severe in all the patients when they first came under notice, and in every case the anæmia was macrocytic and hyperchromic in character, presenting morphological features similar to those of pernicious anæmia of equivalent grades of severity. Leucopenia was marked and platelets were scanty. Reticulocytes were never above 1%. The sternal marrow films when first seen were typical of pernicious anæmia in a stage of relapse, although much liver extract had already been given. With regard to treatment, the authors stress the necessity for energetic measures for maintenance of life by repeated blood transfusions together with the continuance of intensive liver therapy until recovery is obtained. The recovery of all cases in this group emphasizes the importance of persistence in treatment of this type of anæmia. Finally, 2 cases are described of severe granulopenia with moderate anæmia of unknown ætiology, which followed a chronic course of over two years and proved resistant to any form of medical treatment up to the time of writing. These cases showed a cellular normoblastic marrow with arrested myelocyte maturation.

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- ¹ [see BMB 457]

456

THE ANÆMIAS OF PREGNANCY: A Report on the Hæmatological Study of 48 Cases of Pregnancy with a Review of the Literature

by G. A. Elliott, *Journal of Obstetrics & Gynecology of the British Empire*, 51, 198-224, June 1944

This paper reports from the Department of Pathology of the British Postgraduate Medical School a detailed investigation of certain characteristics of the blood in (a) 28 cases of anæmia of pregnancy and (b) 20 control (without clinical anæmia) pregnant women. The investigation included: (i) erythrocyte counts, (ii) leucocyte counts, (iii) hæmoglobin estimations (Haldane), (iv) mean corpuscular volume (Wintrobe, 1930), (v) reticulocyte percentage, (vi) plasma bilirubin (Haslewood & King, 1937), (vii) mean erythrocyte diameter (Price-Jones, 1933), and (viii) erythrocyte fragility (Dacie & Vaughan, 1938).

Results are tabulated for both groups of patients. In the anæmic group, erythrocyte counts ranged from 8.27 to 5×10^6 per mm.³ and hæmoglobin percentages from 32 to 76. Mean corpuscular volumes were from 58 to 98 μ^3 . Plasma bilirubin was within normal limits. Mean erythrocyte diameters in 10 cases ranged from 6 to 7.4 μ .

The chief feature of interest was a significant increase in median corpuscular fragility to normal saline, which was found in both groups. In the anæmic group, it was in some cases beyond normal limits, returning to normal after parturition.

The author discusses normal hæmatological standards in pregnancy and reviews the relevant literature. He suggests the following classification of anæmias of pregnancy:

- i. *Physiological anæmia*
 - ii. *Deficiency anæmia of pregnancy*
 - a. iron deficiency
 - b. megalocytic
 1. pernicious anæmia of pregnancy
 2. megaloblastic anæmia of pregnancy and the puerperium (Davidson, Davis & Innes, 1942)
 - c. mixed iron and pernicious-anæmia-factor deficiency
 - iii. *Unproven*
 - a. acute hæmolytic anæmia of pregnancy
 - b. protein deficiency anæmia of pregnancy (Bethell, 1936)
 - c. vitamin B deficiency anæmia of pregnancy (Elsom, 1935, 1937)
 - iv. *Unclassified.*

types not included in groups i. and ii. but regarded as due to pregnancy
 - v. *Anæmia complicated by pregnancy*
- These anæmias are discussed under the above headings, and the author concludes with a brief consideration of symptom-

atology, treatment, and the influence of anæmia of pregnancy on-maternal and infantile health. There are 124 references to the literature.

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¹ [see *BMB* 451]

457.

MEGALOBlastic ANÆMIA OF PREGNANCY AND THE PUERPERIUM

by L. S. P. Davidson, L. J. Davis & J. Innes, *British Medical Journal*, 2, 31-34, 11/7/42.

Anæmia occurring in pregnancy and the puerperium in temperate climates, apart from the apparent anæmia caused by physiological dilution of the corpuscles resulting from the increased plasma volume of pregnancy (Dieckmann & Wegner, 1934), is usually of the hypochromic iron-deficiency type (Davidson, Fullerton & Campbell, 1935). Very rarely it may be of the classical Addisonian pernicious variety. More often it resembles this type but differs from it in certain features and has been named "pernicious anæmia of pregnancy."

In the present paper, Professor Davidson and his colleagues describe 16 cases of this latter variety of anæmia seen at the Department of Medicine, Edinburgh University. The anæmia was severe in all cases. Analysis of the peripheral blood findings indicated in many of the cases a dual deficiency of liver and iron, for while macrocytosis and a high colour index were frequent, these features were not so pronounced or so constant as in classical Addisonian pernicious anæmia. In some cases the colour indices were below unity. Free hydrochloric acid was also present in the gastric juice of many of the cases. A constant finding, however, was a megaloblastic picture in films made from the sternal marrow obtained by sternal puncture. Accordingly the name "megaloblastic anæmia of pregnancy and the puerperium" has been proposed for this type.

Ten of the cases were temporarily refractory to treatment with liver extract, iron and other hæmatinics, but persistence with such treatment, and maintenance of life with blood transfusions when necessary, eventually resulted in complete recovery in all except two cases in which death resulted from incidental causes.

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458

THE ANÆMIA ASSOCIATED WITH INFECTION

by M. F. Saifi & J. M. Vaughan, *Journal of Pathology and Bacteriology*, 56, 189-197, April 1944

The mechanism of production of anæmia in infections is obscure. The investigation reported in this paper was on the morphology of the blood cells in anæmias associated with infection. The peripheral blood was examined in (i) 10 mild infections (mostly furunculosis), (ii) 20 acute infections, and (iii) 14 chronic infections (of more than 3 months' duration). Bone-marrow and spleen were examined in 15 patients who died—11 cases of acute infection and 4 of chronic infection. Patients receiving a total dose of sulphonamides larger than 1 g. were excluded.

In the mild infections (group i) there was no evidence of anæmia. In 12 acute and 10 chronic infections there was anæmia of a normocytic or macrocytic type, with a colour index never above unity. There was commonly a raised reticulocyte count in chronic cases with severe anæmia. In 12 of the 15 bone-marrow examined there was evidence of increased activity, with leucopoiesis predominating. There was no aplasia of erythropoietic tissue, in which the

predominant cells were primary erythroblasts and normoblasts. The degree and character of the hæmopoietic response appeared to be unrelated to type of infection, severity of anæmia, or age of patient.

On the scanty evidence available, the authors suggest that the anæmia associated with infection is due to interference of hæmoglobin synthesis resulting in arrest of erythropoiesis at the level of normoblasts and primary erythroblasts.

459

ERYTHROBLASTIC ANÆMIA OF CHILDHOOD (COOLEY'S ANÆMIA) IN CYPRUS

by A. L. Fawdry, *Lancet*, 1, 171-176, 5/2/44

Details of 20 cases of this anæmia (Cooley, Witwer & Lee, 1927) occurring in Cyprus are given, with a review of the literature and the differential diagnosis. All the patients were Greek Cypriots aged 6 months to 12 years except one case, which is fully reported, occurring in a man aged 20. Points worthy of special note were: the preponderance in males (15 out of 20 cases); the febrile onset; the occasional history of earth eating; the fact that in spite of gross physical changes, no adverse effect on mental development was found and many children seemed unusually intelligent; mongoloid features were constant in the children over the age of 6 years, and radial striation of the calvarium, although very distinctive when seen, was not as common as simple thickening.

The subjective severity of the disease was entirely a function of the degree of anæmia present, which was remarkably constant over a long period of time. It was always hypochromic and curiously lacked correlation with the age of the child, the date of onset of the illness, the bone-changes, or the number of nucleated erythrocytes in the peripheral blood. Leucocytosis was common in the younger children, but usually absent in the older; on the whole, the percentage of lymphocytes was increased and occasionally the monocytes also. Of the nucleated erythrocytes seen in the peripheral blood, the vast majority were normoblasts, but in most cases there was a small proportion of more primitive cells. Target cells were present in 50% of cases. No evidence of malaria as an aetiological agent was found. The bone marrow showed a constant marked normoblastic reaction. With regard to treatment, none was of any permanent value. Blood transfusions, iron and liver therapy were all given without success.

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460

RED-CELL SUSPENSION TRANSFUSIONS

by L. Watson, *Lancet*, 1, 107-111, 23/1/43

In acute hæmorrhage and shock there is a profound fall in the circulating blood volume, which may be restored by the transfusion of whole blood. In these cases, however, it is not so much the replacement of the erythrocytes that is required, as the restoration of the blood volume. The use of crystalloid solutions such as normal saline results in a transitory beneficial effect, but a more prolonged effect is obtained with colloid solutions. Of the latter, plasma prepared from human blood has been found to be ideal under war conditions, as it can be well preserved without the use of refrigeration and in the dried form can be transported anywhere irrespective of temperature.

In the preparation of plasma the erythrocytes are normally wasted, but there are conditions in which erythrocytes are required but blood volume is normal and there is therefore no need for plasma. The author, working at the *Lee & General Infirmary*, has made use of the waste erythrocytes from a Regional Transfusion Centre in the treatment of anæmic patients. This is no new form of therapy as it was used as early as 1918 by Robertson, in 1937 by Castellanos & Riera, and in the present war by Beumer & Schwartz (1939), MacQuaide & Mollinson (1940), Whitby (1941), Vaughan (1941), Davidson & Stewart (1941), and Williams & Davy (1941).

In the present paper the author reports the results of 46 transfusions of concentrated erythrocytes to 22 adult

patients, 13 suffering from anæmia following hæmorrhage, 5 from chronic anæmia and 4 miscellaneous cases.

Donors were relieved of 440 cm.³ of blood which was collected in bottles containing 100 cm.³ of 3 % sodium citrate solution. This blood was allowed to stand for periods varying from 3 to 12 days at 4° C. The supernatant plasma was then siphoned off and the remaining mass was filtered through a gas mantle. The concentrated erythrocytes from several bottles were then pooled to produce a suspension containing about 290 cm.³ of erythrocytes, 157 cm.³ of plasma, and 75 cm.³ of citrate solution per bottle and furnishing about 18 grams of hæmoglobin per 100 cm.³ of suspension. This suspension could be given to the patient by the ordinary gravity drip method, but if it was more concentrated it was found necessary to provide some form of mechanical pump to maintain a constant flow. The author used only cells from Group O blood, but stresses the importance of performing a thorough cross-matching of donor's and recipient's bloods before transfusion is commenced. Transfusions were administered with the standard *Medical Research Council* equipment.

In general, the results of the treatment appeared clinically to be as good as if whole blood had been used. No systematic observations were made on the survival of transfused erythrocytes, but it was noted in one case of aplastic anæmia that cells which had been stored for 6 to 10 days survived in the circulation for 40 days, while cells stored for 12 or 13 days survived only 14 days.

If the pre-transfusion hæmoglobin level, the body weight of the recipient, and the desired rise of hæmoglobin are known, the transfusion volume can be accurately prescribed, as in the following example: Initial Hb 5 grams per 100 cm.³ Body weight 55 kg. Desired Hb level after transfusion, 15 g./100 cm.³. Hb concentration of erythrocyte suspension, 20 g./100 cm.³. Then blood volume is approximately $55/11 = 5$ litres. Total Hb in body before transfusion is $5000 \times 5/100 = 250$ grams. Total Hb in body after transfusion is $5000 \times 15/100 = 750$ grams. Therefore Hb to be added is 500 grams, and this is contained in 2500 cm.³ of the erythrocyte suspension. This method of calculating dosage is ially valuable where children are concerned.

e author recommends that (i) concentrated erythrocyte nsions should be used when the object of treatment is store the oxygen-carrying capacity of the blood, (ii) erythrocytes should not have been stored for long, (iii) Group O l should be used for making the suspension, (iv) suspension should not be warmed before administration, (v) for nsions containing more than 18 g. Hb per 100 cm.³ a ell's (1939) pump should be incorporated in the transfusion apparatus, (vi) the transfusion volume should be calculated in terms of Hb, (vii) cases of refractory anæmia should have repeated erythrocyte suspension transfusions, (viii) not more than 100 cm.³ of a suspension should be transfused to an out-patient on any one occasion.

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461

THE TRANSFUSION OF CELL CONCENTRATES

by A. L. Goodall, *Glasgow Medical Journal*, 141, 161-171, June 1944

The author reports 100 transfusions of concentrated (average 9×10^6 per mm.³) erythrocytes performed in the Glasgow and West of Scotland Blood Transfusion Service at Glasgow Royal Infirmary. The cases were of a surgical (loss of blood) and medical (blood disorders) nature and included most types for which transfusion of blood is indicated. After 1 accident in a patient with much fatty infiltration of the myocardium, administration by the drip method was used invariably, at a rate of about 60 drops per minute. There was no difficulty in infusing the concentrate by this method. There was a low incidence of reaction.

The changes resulting from the transfusions, expressed as mean rises per cells obtained from 500 cm.³ blood, were: hæmoglobin, 1.49 g. per 100 cm.³; erythrocytes, 480,000 per mm.³; packed cell volume, 3.49 %.

The author regards erythrotransfusion as a safe and useful measure which is in some cases preferable to whole blood transfusion.

Other Blood Changes

462

THROMBOCYTOPENIC PURPURA

by H. Evans & K. M. A. Perry, *Lancet*, 2, 410-413, 2/10/43

This review deals with 75 cases of thrombocytopenic purpura treated at the *London Hospital* between 1927 and 1938. Thirty of the cases (40 %) occurred before the age of 15 years and these were equally divided between the sexes. In ten of them, there was spontaneous recovery and, of the remaining twenty, splenectomy was successful in 5 males and unsuccessful in 4 females. One patient died with septic meningitis following chronic mastoiditis and 5 died as a direct result of the disease during the period of observation. The remaining 5 cases could not be traced. The analysis shows that this is a serious disease with a high mortality (16 %), but that 10 cases out of the 30 (5 of each sex) recovered spontaneously.

Of the 45 cases (60 %) which occurred after puberty, 38 were females, only one of whom made a spontaneous recovery. Splenectomy was successful in only 7 out of 13 females, the mortality during the period of observation being as high as 40 %. It is evident that the disease is much more severe in women than in children, for in women the mortality is high (16 deaths in 38 cases) and the likelihood of spontaneous recovery small (1 case out of 38). Half of the deaths were due to subdural hæmorrhage.

The disease in males after puberty seems to be less severe although it is unwise to judge from the 7 patients in this series, only one of whom died—again from subdural hæmorrhage. One patient died following thyroidectomy after he had been cured of thrombocytopenic purpura by splenectomy. One case remained "unchanged" and one could not be traced. There were two spontaneous recoveries and two patients were cured by splenectomy.

In the whole series splenectomy was successful in 7 out of 7 males and in 7 out of 17 females. There were three operative deaths. Splenectomy is most successful in males before puberty and least successful in adult females, but it may at any age be a life-saving measure and is sometimes advisable in the hope of preventing subdural hæmorrhage.

463

THE SOURCES OF BLOOD PLATELETS AND THEIR ADHESIVENESS IN EXPERIMENTAL THROMBOCYTOSIS

by H. P. Wright, *Journal of Pathology and Bacteriology*, 56, 151-159, April 1944

A rise in the number of circulating thrombocytes in rabbits and guinea-pigs after intravenous injection of pyridine was described by Perroncito (1920), who considered that there was an increased production and not merely a release from storage. Binet & Kaplan (1927) observed an increase in thrombocytes after injection of adrenalin in intact but not in splenectomised dogs, and suggested that the increase was due to release from a contracting spleen. Wright (1942) found that the thrombocytosis in man after surgical operations was associated with increased adhesiveness of the thrombocytes.

The work reported in the present paper was undertaken to determine whether experimental thrombocytosis was accompanied by increased adhesiveness. Methods of counting thrombocytes and measuring their adhesiveness have been described in earlier papers (Wright, 1941, 1942). The experimental procedures used in the present investigation are described and results are tabulated. In the intact rabbit, thrombocytosis was provoked both by pyridine and adrenalin, but only after pyridine was there an increased adhesiveness. In splenectomised rabbits, adrenalin had no effect, while

pyridine evoked a response which was minimal during the period when the increase in numbers and adhesiveness of the thrombocytes induced by the surgical trauma was maximal. As the thrombocyte count returned to normal, the effect of pyridine increased.

The authors conclude from these and other considerations that adrenalin produces a release of mature thrombocytes from the spleen, while pyridine increases the production of new thrombocytes from bone-marrow. It is suggested that the increased adhesiveness after pyridine and after surgical trauma is due to a reduction in the average age of the circulating thrombocytes and not to a mere increase in their number.

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Wright, H. P. (1942) *J. Path. Bact.* **54**, 461

464

HÆMORRHAGIC DISEASE OF THE NEWBORN

by E. B. S. Scobbie, *Archives of Disease in Childhood*, **17**, 175-186, December 1942

In this paper from the Department of Pædiatrics, Glasgow University, the criteria necessary for the diagnosis of hæmorrhagic disease of the newborn are discussed with reference to the literature. The author accepts Clifford's (1935) definition, "spontaneous internal or external hæmorrhage in the newborn infant in the absence of trauma, infection or other definite disease."

The records of 167 cases of hæmorrhage in the newborn infant were studied, 146 of which fall strictly within the bounds of the above definition. Eighteen of these cases were examined personally by the author. Analysis of the incidence rate corresponds in most respects with previous reports in the literature. The cases have been grouped into 3 classes according to the percentage of hæmoglobin:

Severe	Hb under 80 %
Moderate	Hb 80 %-100 %
Mild	Hb over 100 %

Observations were made on the level of prothrombin in the blood in 15 cases of hæmorrhagic disease. The method used was Reid's (1941) modification of Quick's method and the level of prothrombin is expressed as the prothrombin index (Illingworth, 1939), which is

$$\frac{\text{normal prothrombin time}}{\text{patient's prothrombin time}} \times 100.$$

The following results were obtained:

In 7 severe cases	prothrombin indices of	70 %, 43 %, 35 %, 25 %, 20 %, 14 %, 5 %
In 3 moderate cases	"	" 73 %, 40 %, 18 %
In 5 mild cases	"	" 65 %, 60 %, 58 %, 45 %, 31 %

A marked variation of the prothrombin index was noted and there was a lack of correlation between the hypoprothrombinæmia and the severity of the case.

The prothrombin indices of 75 healthy newborn infants were estimated as a control. On the first day of life 24 %, on the second day 12 %, and on the third day 8 % had prothrombin indices under 50 %, as compared with 67 % of the cases of hæmorrhagic disease. However, the prothrombin index in hæmorrhagic disease is not constantly lower than in physiological hypoprothrombinæmia.

The effect of subcutaneous blood and vitamin K injections on the prothrombin index in physiological hypoprothrombinæmia and in hæmorrhagic disease was determined. Subcutaneous blood had practically no effect, whereas vitamin K produced a constant elevation although there was sometimes a delay in its action. Blood transfusion in 4 cases of hæmorrhagic disease caused a considerable increase of prothrombin.

The author attempts to analyse the effect of treatment on the mortality rate in this series. The relatively small number of cases treated with vitamin K makes this difficult. Results seem to show that intravenous blood is superior to vitamin K or subcutaneous blood as a therapeutic agent. Vitamin

K therapy seems to cause a lower mortality rate than does treatment with subcutaneous blood.

The view that vitamin K deficiency explains the ætiology of hæmorrhagic disease is not supported by these findings, although it appears to be an important factor.

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465

ELLIPTOCYTOSIS IN MAN ASSOCIATED WITH HEREDITARY HÆMORRHAGIC TELANGIECTASIA

by J. B. Penfold & J. M. Lipscomb, *Quarterly Journal of Medicine*, **12**, 157-167, July 1943

These authors review the literature on elliptocytosis and on hereditary hæmorrhagic telangiectasia and record the findings in a Jewish family of 32 members in 4 generations, in 5 of whom there was evidence of telangiectasia and elliptocytosis, while in 4 there was evidence of telangiectasia alone.

Those members showing elliptical erythrocytes had in addition signs of hæmolytic icterus, a delayed direct van den Bergh reaction, without an increase in fragility. Three members showed a slight degree of secondary anæmia, while 1 had an increase in erythrocytes. All 5 had over 90 % of oval erythrocytes in their blood, and although the percentage varied from person to person it seemed to be quite constant for the individual concerned. The wet film gave consistently higher percentages than the dry film and the change in the wet count on keeping was not significant (cf. sickle-cells). The authors believe that the count done on the dry blood film is not reliable, as the number of oval cells varied with the film, particularly with its thickness. The oval cells were most numerous where the film was thickest, becoming fewer as the film became thinner.

Blood from three of the subjects was diluted 200 times in hypertonic (1.2 %) and hypotonic (0.6 %) saline, and daily counts of the total and oval erythrocytes were made. In the hypertonic saline, the absolute number of oval erythrocytes diminished to a minimum at about the third or fourth day, rising again later (about the fifth or sixth day) to a figure not as high as the original. There was a diminution in the total count, gradual at first and more rapid later. Corresponding to the absolute diminution of the oval cells at about the third or fourth day, there was at that time an absolute increase in the cells which appeared circular. Similar results were obtained in the hypotonic saline solution. These observations showed that the oval shape could be changed by alteration in the physical characters of the medium.

Findings from the following hæmatological studies were normal: erythrocyte fragility test, total leucocyte count, differential leucocyte count, platelet count, bleeding time, coagulation time and Wassermann and Kahn reactions.

It is suggested that the appearance of elliptocytosis in association with hereditary hæmorrhagic telangiectasia could be satisfactorily explained if both were regarded as atavistic mutations. This view has been put forward by others in connexion with elliptocytosis and rests chiefly on the fact that most vertebrates lower than the mammals have oval erythrocytes. This is evidently the primitive type of erythrocyte.

It is not impossible that telangiectasia is also a reference back to an amphibian state in which the mucous membranes of mouth and throat regions and the skin are accessory breathing surfaces and therefore highly vascular.

The authors draw particular attention to the icteric phenomena present in their cases of elliptocytosis and point out that this feature, although seldom mentioned in text books, was present in not less than 12 % of the recorded cases. The nature of the mechanism causing the increased hæmolysis is not known.

466

TROPICAL EOSINOPHILIA

by R. J. Weingarten, *Lancet*, **1**, 103-105, 23/1/43

Under this title, the author describes 81 cases of a new syndrome characterised by severe spasmodic bronchitis, leucocytosis and very high eosinophilia. The condition is

common in India and particularly affects people living near the sea. It has no apparent relation to tuberculosis or any other disease, and begins with lassitude, fever rising as a rule to 100–101° F. [about 37·9–38·3° C.] in the evening, anorexia, and usually appreciable loss of weight within a short time. After about a week of these symptoms, a dry, ineffective cough develops, with exacerbation at night. The patient's sleep is interrupted by paroxysms of coughing, and these are often accompanied by wheezing sounds audible at a distance. Gradually he develops expiratory dyspnoea which even persists during the intervals between attacks of coughing, and this stage lasts many weeks. In some cases, however, severe attacks of typical bronchial asthma occur regularly every night, usually between 1 and 5 a.m.; but the restlessness, sense of suffocation and anxiety are not so alarming as in genuine asthma. In the day-time the patient is comparatively free from coughing and breathlessness. After some weeks the temperature becomes subfebrile, and there is no further loss of weight. General weakness decreases to some extent, but more or less violent paroxysms of coughing, and in many cases asthmatic attacks, persist at night, and if no treatment is given become chronic. Physical signs, during the more typical attacks, resemble those of bronchial asthma. If there is any expectoration, the sputum is scanty, tenacious and glassy. On microscopic examination, Charcot-Leyden crystals or Curschmann spirals are rarely seen, but clumps of eosinophils are often found. During the febrile period the spleen is moderately enlarged, extending 3–5 cm. below the costal margin; it is hard, smooth and not tender. The x-ray picture of the lungs during the febrile period shows a distinctive disseminate mottling of both lungs, the average single focus being about the size of a split pea with moderate intensity of its central shadow and ill-defined, blurred outlines. These foci are more numerous and usually slightly larger in and near the hilar regions, and commoner in the bases than in the apices; they are not confluent but both lungs are equally affected. Adrenalin gave prompt relief in the spasmodic attacks and a course of injections of arsenicals was found to be a specific remedy.

[Carter, H. F., Wedd, G. & d'Abrera, V. St. E. (1944), *Ind. med. Gaz.* 79, 163] have recently reported from Ceylon similar cases which were associated with the presence of parasites, including species of *Tyroglyphus*, *Carpoglyphus*, *Glyciphagus*, *Cheyletus* and *Arsonemus*, in the sputum. They suggest that "tropical eosinophilia" may be due to infestation by these parasites.]

167

TROPICAL EOSINOPHILIA

by B. G. Parsons-Smith, *Lancet*, 1, 433–434, 1/4/44

The author reports a typical case of tropical eosinophilia, as recently described by Weingarten (1943), occurring in an English airman in Egypt. After the first two injections of neoarsphenamine, there was a recrudescence of the condition, a common occurrence in Weingarten's cases, but subsequent injections produced a dramatic, rapid and permanent cure.

REFERENCE

¹ Weingarten, R. J. (1943) *Lancet*, 1, 103

¹ [see *BMB* 466]

468

AGRANULOCYTOSIS AND APLASTIC ANÆMIA AFTER ARSPHENAMINES

by J. W. Ferguson, *Lancet*, 1, 334–337, 11/3/44

Since the introduction of organic arsenicals in the treatment of syphilis, there have been a number of reports of toxic effects on the hæmopoietic system, although in view of the widespread use of these compounds this would appear to be a relatively rare complication.

The author gives case records and details of blood and bone-marrow findings in 6 soldiers and seamen who developed blood dyscrasias after neoarsphenamine treatment. In the first 5 cases there was agranulocytosis, and the sixth showed depression of all marrow elements. Three of the cases were fatal, and in the 3 which recovered an increased absolute number of monocytes was found. The first 5 cases had received an average of 5 injections of neoarsphenamine, the average total dose being 2·1 g. The sixth patient had received 5·7 g. of neoarsphenamine and 2·0 g. of bismuth.

The more favourable prognosis in cases in which there is

an increase of monocytes in the peripheral blood has previously been remarked (Beck, 1933; Rosenthal & Abel, 1936; Reznikoff, 1938).

The author is of the view that pentnucleotide assisted recovery in the 3 non-fatal cases.

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Hæmoglobinometry

469

ESTIMATION OF HÆMOGLOBIN BY THE ALKALINE HÆMATIN METHOD

by J. W. Clegg & E. J. King, *British Medical Journal*, 2, 329–333, 19/9/42

The authors of this paper, an Area Clinical Pathologist in the British Emergency Medical Service (Ministry of Health) and a Reader in Pathological Chemistry (University of London), discuss hæmoglobinometric methods in current use and give particulars of a new technique employing alkaline hæmatin as a standard.

The hæm-pigments circulating in the blood may be divided into an active fraction (reduced hæmoglobin and oxyhæmoglobin) and an inactive fraction (chiefly carboxyhæmoglobin and methæmoglobin). A satisfactory method of estimating hæmoglobin should measure both fractions. The Haldane and acid hæmatin methods may not measure total pigment with the degree of accuracy desirable. Commercial standards are often unreliable and may fade. The pyridine hæmochromagen method is rejected by the authors because of the objectionable nature of the reagents employed.

Criteria of a satisfactory method are described. These include the measurement of total pigment, reasonable accuracy, simplicity, the use of non-toxic reagents, and some permanent and easily reproducible standard. The alkaline hæmatin method of Wu eliminates errors which arise in the acid hæmatin procedure due to lipids, the colloidal nature of acid hæmatin, and the presence of inactive hæmoglobin. Alkaline hæmatin has the advantage of being a true solution and is easily prepared both from hæmoglobin and from crystalline hæmin. Hæmin is easy to prepare in a pure state from hæmoglobin, and its iron content may be estimated with accuracy. Thus it appeared to satisfy the authors' criteria for a suitable standard, and was investigated for this purpose.

Sixteen samples of crystalline hæmin were prepared from ox and human bloods and the iron content of each was determined. Solutions of alkaline hæmatin were prepared from each sample. The specific extinction coefficients were found to agree closely. The intensity of colour was proportional to the concentration of hæmin iron, and impurities failed to influence the colour.

Several forms of hæmoglobin occur in normal blood, some of which are resistant to alkali denaturation. Whatever the proportion of alkali-resistant hæmoglobin in a blood sample, if a 1 in 100 dilution in decinormal soda is prepared and placed in a boiling-water bath for five minutes, all the hæmoglobin is converted into alkaline hæmatin. Similar treatment converts all inactive forms of hæmoglobin into alkaline hæmatin. The colour developed is not significantly influenced by the amount of lipid or plasma in the sample.

Determination of hæmoglobin in blood samples, based on the assumption that 1 mg. hæmin iron in the standard was equivalent to 1 mg. hæmoglobin iron in the test, yielded results uniformly about 30% higher than determinations based on the oxygen-carrying power of the same sample. It was then found that solutions prepared from hæmin and blood gave colours whose absorption curves differed slightly in the red portion of the spectrum.

Samples of human and ox hæmoglobin were prepared and their iron content was determined. Solutions of alkaline hæmatin were prepared from each sample and their specific extinction coefficients and absorption curves were determined. The curves derived from the hæmoglobin solutions were identical with that from blood, and the colour produced was

30 % higher than would be anticipated from the iron content, when compared with hæmin standards.

Thus hæmin is not a theoretical standard in the sense that four molecules of hæmin should give the same colour as one molecule of hæmoglobin; but it can be employed satisfactorily as an artificial standard. The colours of the solutions are almost identical in the concentrations used for the test, and are matched with ease and accuracy. The standard appears to be unchanged during several months.

Details of methods for the estimation of total hæmoglobin, using hæmin as a standard, are given, together with instructions for the preparation of standard solutions equivalent to 100 % of the Haldane, Sahli, and Haden scales.

The authors had employed this method for many months and found it to give excellent results. Where many determinations were made daily it was quicker and more reliable than other methods they had used.

470

A SIMPLE INEXPENSIVE PHOTOELECTRIC HÆMOGLOBINOMETER

by G. H. Bell & E. Guthmann, *Journal of Scientific Instruments*, 20, 145-146, September 1943

This paper, from the Institute of Physiology, University of Glasgow, describes a simple and inexpensive colorimeter which is unaffected by variations in the light source or photocell characteristics. To avoid calculating the extinction-coefficient (E) at each estimation, a pointer attached to the lamp moves along a scale which is calibrated directly in E values obtained by a simple calculation. With the lamp at the maximum distance D_0 from the photocell and with water alone in the glass cell, the galvanometer deflexion is noted; blood is added to the water in the glass cell and the lamp is pushed up to a distance D_1 from the photocell where the photocell current is the same as before. The $E = \log D_0^2/D_1^2$. Details of the construction and calibration as a hæmoglobinometer are given. All the component parts are readily available, and inexpensive. A modification of the simple instrument is also described using a balanced circuit with two photocells in parallel opposition to cancel out the light fluctuation when the lamp is supplied from either direct or alternating current mains.

Plasma and its Constituents

471

PLASMA PROTEIN VALUES IN INFANTS

by E. M. Hickmans, E. Finch & E. Tonks, *Archives of Disease in Childhood*, 18, 96-97, June 1943

This report from the *Children's Hospital*, Birmingham, deals with the results of plasma protein determinations in 20 premature babies and 180 normal full-term infants and young children up to 40 weeks old attending infant welfare centres. Estimations were made by a micro-Kjeldahl method, followed by Nesslerization, on specimens of 0.01 ml. of plasma obtained from heparinized blood from a heel prick. [Whether the amount of heparin used was sufficient to affect the nitrogen figures is not stated.]

It was found that in the first 2 weeks of life the infant has between 4 and 7 g. per 100 ml. plasma protein, although "in the majority of instances" the value was below 6 g. per 100 ml. Values for premature infants in the first four weeks of life were between 3.7 and 5.4 g. per 100 ml. The range for full-term infants over 2-3 weeks old was 4.7-7.4 g. per 100 ml. In infants over 10 weeks old "most of the values lie in the upper half of this range, viz. between 6 and 7.4 g. per 100 ml."

472

THE EFFECT OF THE PLASMA PROTEINS UPON THE SEDIMENTATION RATE OF HUMAN BLOOD

by C. M. Gordon & J. R. Wardley, *Biochemical Journal*, 37, 393-397, September 1943

It has been known for some time that the sedimentation rate of erythrocytes is determined in part by the protein constituents of the plasma. No clear correlation has, however,

been found between the sedimentation rate and the concentrations of the various plasma proteins although Frazer & Rennie (1941) found a fall in plasma albumin and, to a smaller extent, increase of fibrinogen, to be associated with an increased sedimentation rate. In this paper from the Pathological Department of the *Lake Hospital*, Ashton-under-Lyne, the problem has been approached, by building up 'pathological plasmas' with protein fractions prepared from normal plasma, and observing the behaviour of normal cells suspended in them. In most cases the protein concentrations of the solutions were about 3 g./100 ml. of 0.85 % NaCl and the cell volume suspension was 20 %. Sedimentation was observed in Westergren tubes, usually at the end of 1 hour.

The most rapid sedimentation rates were found with fibrinogen and euglobulin, the order being fibrinogen (100 mm. in 1 hour) > euglobulin > globulin > albumin (1.5 mm. in 1 hour). The results were, however, affected by the treatment to which the protein fractions were submitted during their isolation. The "slower" proteins when mixed with "fast" proteins did not merely reduce the sedimentation rate by acting as a diluent. Nucleoprotein, albumin and the "globoglycoid" fraction of albumin, retarded the sedimentation rate of cells suspended in solutions of fibrinogen. Sedimentation was slightly accelerated by total globulin and its euglobulin fraction. Sedimentation can take place in the absence of fibrinogen which, however, plays the chief part in determining the rate.

From two experiments it was concluded that an artificial mixture of proteins from "normal" plasma can closely resemble naturally-occurring pathological plasma in its effect upon sedimentation. By altering only the globulin fractions in "artificial tuberculous plasma" the sedimentation rate could be changed from 94 to 26 mm. When crystalalbumin was substituted for the total albumin of "artificial nephritic plasma" the sedimentation rate increased from 15.0 to 145 mm.; when globoglycoid was substituted it was reduced from 15.0 to 1.0 mm.

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473

CHANGES OCCURRING IN PLASMA AND SERUM ON STORAGE AND THEIR PHYSIOLOGICAL EFFECTS

by H. P. Gilding & M. E. Nutt, *Journal of Physiology*, 102, 446-470, April 1944

These experiments reported from the Department of Physiology in the University of Birmingham deal with the toxic effects in cats following the rapid injection of plasma or serum, either human or from cats, which has been stored for over 14 days. From 0.5-2 ml. of plasma or serum, which had been stored for periods up to 18 months, was rapidly injected warm, usually into the internal saphenous vein of cats anaesthetised with "dial." Injection at the rate of 0.6 ml./kg./minute was followed by similar but much less striking effects. No toxic manifestations followed injection of fresh (prepared within 45 minutes of bleeding) plasma.

Although the cat was found to be the most suitable animal in which to demonstrate the toxic properties of stored serum and plasma, toxic reactions were observed in dogs, in rabbits and in two apparently healthy men. In the animals, records were taken of systemic and pulmonary arterial pressure, venous and intrapleural pressure, intestinal and limb volume, and total and differential leucocyte count.

The following reflex effects were noted both in anaesthetised and in decerebrate cats within 20-30 seconds of giving the injection—vagal inhibition of the heart with actual arrest in some cases, profound fall in the systemic and an increase in the pulmonary arterial pressure, altered respiration which sometimes ceased, increased peristalsis, micturition, defecation, vomiting, pupillary constriction, opisthotonos and a leucopenia which was followed after some hours by leucocytosis. Necropsy revealed that the capillaries of the lungs and suprarenals and, to a minor extent, of the liver were packed with polymorphonuclear leucocytes, a finding which has been described previously in anaphylaxis, but it was established that this phenomenon was not responsible for the reflex response to plasma injections. Injection of plasma into the splenic vein was not followed by the massive reflex effects but still produced a leucopenia suggesting that the liver can protect the animal from the toxic effects of stored

plasma, most of which are abolished by vagotomy or by atropine. Cross-circulation experiments supported the finding that the effects mentioned above were reflexly produced. It was established that the vagus, although the most important, cannot be the only sensory nerve involved in the reflex, which may be initiated by pressure changes in the pulmonary circulation.

All these phenomena, which resemble those occurring in anaphylactic shock, were shown to be the result of storing plasma or serum for some 3–4 weeks. The clotting process seems to play no part in the development of toxicity and the breakdown of platelets is not responsible. The activity is associated with an albumin which is precipitated by 66–75 % saturation with ammonium sulphate (and by other methods) and represents not more than 8 % of the total protein of the original serum or plasma. The different conditions described following the injection of stored human or cat plasma into cats "may merely represent different methods of eliciting a general physiological response to the injection of foreign matter into the circulation."

474

A STUDY OF THE ACCURACY OF SERUM PROTEIN ESTIMATIONS AND OF DIURNAL VARIATIONS IN THEIR LEVEL

by M. Dyson & G. Plaut, *British Medical Journal*, 2, 6–7, 3/7/43

In this investigation from the North-West London Blood Supply Depot, serum protein was determined by the micro-Kjeldahl method of Pregl (1937) and by the method of King and his associates (1937, 1942) which employs Kjeldahl digestion followed by Nesslerization and colorimetric determination. In order to test and compare the two methods, ten estimations on each of ten samples of the same serum were made, the procedure being repeated with each of ten different sera with protein values between 6.03 and 7.40 g. per ml. giving 100 estimations in all by each method. The results obtained by both methods were analysed separately in two ways: (a) by computing the grouped differences (b) by determining the average standard deviations. Both methods of treatment showed that the micro-Kjeldahl method is the more accurate. With the latter method, values of less than 0.15 g. per 100 ml. should be ignored, changes of 0.15 to 0.20 are probably, and those over 0.20 are almost certainly significant, whereas with King's method a difference must exceed 0.40 g. per 100 ml. before it be considered significant.

To determine whether there is a significant diurnal variation in serum protein under "ordinary working conditions" ten samples were taken at two-hourly intervals between 9 a.m. and 6 p.m. from 20 healthy persons of ages between 18 and 50. No great variations were found by either method. This finding does not agree with the published results of other authors, but Dyson and Plaut emphasise "that many variations in serum protein recorded in the literature are not significant and that changes in the character of tissue and circulating fluid cannot be calculated from changes in serum protein unless accurate methods with a known technical error are employed and standard conditions of posture and exercise adopted."

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475

FIBRINOGEN DEFICIENCY AS A FACTOR IN HÆMORRHAGIC DISEASE

by E. C. Allibone & H. S. Baar, *Archives of Disease in Childhood*, 18, 146–153, September 1943

This paper, from the Children's Hospital and the Department of Pædiatrics at Birmingham University, contains the description and discussion of two fatal cases of fibrinogen deficiency in infants. A review of the literature showed that some fifteen cases had previously been reported, ten of which occurred in infants or children. In five of these cases, and

in one now reported, a low thrombocyte count was associated with a low plasma fibrinogen. The authors accept the view that fibrinogen deficiency can exist in two forms. Congenital fibrinopenia is characterized by a tendency to bleed from birth, although in cases which survive with a continuously low or absent plasma fibrinogen, the bleeding becomes periodic for reasons which are at present not understood.

The authors' first case belonged to this group, the ætiology of which is quite unknown. The plasma fibrinogen was 0.11 g. per 100 ml. and the coagulation time exceeded 4 hours. The second case was regarded as belonging to the second group—acquired transient afibrinogenia following congenital obliteration of the bile ducts, complete obstructive jaundice, and biliary cirrhosis. The fibrinogen was initially nil but reached 0.34 g. per 100 ml. 3 days before death. It was considered that evidence exists for the production of fibrinogen by the bone-marrow as well as by the liver, which may explain the thrombocytopenia found in some cases, the gradual increase in plasma fibrinogen in the second case with extensive liver damage, and the fact that gross liver damage can exist with normal plasma fibrinogen. The relationship between prothrombin, fibrinogen, and other coagulation factors is discussed.

Circulatory Dynamics

476

SYNCOPE IN BLOOD DONORS

by F. C. Poles & M. Boycott, *Lancet*, 2, 531–535, 7/11/42

In this paper from the British Army Blood Transfusion Service the authors have analysed the causes of fainting in blood donors. Of their first 10,000 donors only 2.9% fainted, but of these 14% collapsed after their return to work, an accident which might have serious consequences. All donors were kept lying down for 15 minutes after bleeding and were given a cup of tea and a biscuit, and they then remained sitting for another 5 minutes before returning to their work. The common clinical findings of those who fainted were pallor, sweating, slow breathing and a low blood pressure. The systolic pressure may still be below 100 mm.Hg. an hour after bleeding and may take 2 hours to return to normal. Fainting affected both sexes equally but was much commoner in young people. Greenbury (1942), however, found that young female donors were most likely to faint than males especially in the age-group 18–25 years.

The rate of withdrawing blood and the heat and humidity of the surroundings did not influence the incidence of fainting, nor was it affected by moderate anæmia or low blood volume. On the other hand, there was a definite connection between the amount of blood withdrawn and subsequent syncope, and fainting was much more common in donors who had given more than 440 cm.³ of blood. All the donors who fainted had a low blood pressure after bleeding and in some the blood pressure fell much more rapidly after 440 cm.³ had been removed. In the normal donor, the systolic pressure hardly fell at all and had started to rise 15 minutes after the operation, but nearly all those who suffered from delayed syncope still had a falling systolic pressure after 15 minutes. The donors who were subject to delayed fainting attacks also showed an alteration in blood pressure when they sat up after the operation, the systolic pressure falling while the diastolic rose slightly at first and then followed the systolic pressure. This phenomenon differs from true orthostatic hypotension in which there is a simultaneous fall in both systolic and diastolic pressures. In general the delayed fainting attacks resembled vaso-vagal attacks which have been described by Sir Thomas Lewis (1932).

The measures advocated by the authors for the prevention of syncope in blood donors are as follows:

- Avoidance of bleeding when the donor is fatigued.
- Provision of food and fluid before as well as after taking the blood if the donor's last meal has been taken more than 4 hours previously,
- Not taking more than 440 cm.³ of blood (not more than 350 to 400 cm.³ if the donor weighs less than 7 stone [44 kg.]).

iv. Administration of 1 litre of normal saline, before bleeding, to donors who are likely to be dehydrated, e.g., those coming from hot workshops. This was found to effect a marked reduction in the number of these workers who fainted.

v. Taking a series of blood pressure readings on all donors who have fainted on a previous occasion. If the systolic pressure falls after bleeding and continues to fall after sitting up, the donor should be given further rest even if he feels well.

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477

VENOUS PRESSURE DURING VENESECTION AND BLOOD TRANSFUSION

by J. F. Loutit, M. D. Mollison, & E. D. van der Walt, *British Medical Journal*, 2, 658-661, 5/12/42

In man few observations have been made on the changes in venous pressure during the withdrawal and administration of blood, although Altschule & Gilligan (1938) observed that transfusion of saline at rates above 20 cm.³ a minute caused a rise in venous pressure proportional to the amount of fluid given. Immediately after the end of such transfusions the venous pressure fell rapidly, reaching the original level within 20 minutes. Murphy (1941), also using saline, noted a rise in venous pressure during the first half hour of transfusion followed by a fall which he attributed to vasodilatation.

In the present investigation, from a London Blood Supply Depot, venous pressure changes (recorded by inserting a 16 S.W.G. intravenous needle into an antecubital vein and connecting the needle with a manometer) were observed in healthy individuals during venesection, in unselected hospital patients during transfusion, and in a group of patients with pulmonary disease, before, during, and after transfusion.

Venesection was performed on 20 healthy blood donors, 430 cm.³ of blood being removed from each over an average period of 4 minutes. In every case there was a fall in venous pressure during bleeding ranging from 13 to 80 mm. of water with an average of 43 mm. This fall usually commenced after 100 to 200 cm.³ of blood had been withdrawn, continuing until the end of the venesection. After completion of bleeding the venous pressure rose again slowly, but in no case did it reach the pre-bleeding level by the end of 30 minutes. The changes in blood-pressure and pulse-rate were variable.

The venous pressure was estimated during the transfusion (administered by gravity with the *Medical Research Council* apparatus) of 30 unselected hospital patients who were given 500-1000 cm.³ of citrated blood at rates varying from 7-45 cm.³ a minute (average 18.5 cm.³ per minute). In 19 out of 30 cases the venous pressure rose by more than 20 mm. of water during the transfusion, but only in 6 cases did the rise exceed 50 mm. of water. There was apparently no constant relationship between the rate of transfusion and the rise of venous pressure, although proportionately more cases showed a rise at the faster rates. In the cases in which the venous pressure rose, the increase occurred progressively during the transfusion and was approximately proportional to the amount of blood transfused. Contrary to the findings of Altschule & Gilligan, however, it was observed (in 10 cases) for 10 to 30 minutes after transfusion that, while the venous pressure fell gradually, it did not return to the pre-transfusion level during the period of observation. No constant changes in blood-pressure or in pulse-rate were observed in 26 cases before and after transfusion. Only 3 of the 30 cases showed obvious signs of peripheral vasodilatation during transfusion.

In 13 patients suffering from various chronic chest diseases, who were transfused with 800 to 1000 cm.³ of blood at an average rate of 23 cm.³ a minute, both the venous pressure and the vital capacity were measured at the beginning and end of transfusion. Six of the 13 cases showed a rise in venous pressure during transfusion and all but one a reduction in vital capacity at the end of transfusion (average reduction 230 cm.³). The respiratory rate was increased in 3 of the patients by more than 4 respirations per minute but only 2 patients complained of symptoms.

The authors discuss the mechanism of production of the

rise in venous pressure and the reduction in vital capacity which occurred during these transfusions, and they conclude that they are not due to cardiac embarrassment but merely indicate that the larger veins and the lung capillaries are accommodating the extra fluid.

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478

FAINTING IN BLOOD DONORS

[Unsigned] *British Medical Journal*, 1, 279-283, 26/2/44

This is the text of a report to the *Medical Research Council* prepared by a Subcommittee of the Blood Transfusion Research Committee. The large-scale bleeding of donors that has been undertaken since the outbreak of war gave rise to an interest in the nature and causation of fainting during or after the donation of blood. Such incidents are a source of delay and inconvenience, and an investigation was instituted with the objects (i) of identifying factors associated with fainting in blood donors and (ii) of determining the frequency of delayed faints. A record card was designed and provided to bleeding centres in England and Scotland. Blood transfusion officers were asked to complete a card for (a) every donor who fainted during a bleeding procedure, (b) the next donor bled by the same officer (these constituted an unselected group who did not faint).

The data received were submitted to a statistical analysis, and are summarized in 11 tables in this report. Figures were obtained for a total of 697 donors of whom 362 fainted and 335 did not. The incidence of fainting appeared to be lower in men than in single women, and slightly lower in single than in married women. There was no evidence that age, length of waiting period at the centre before bleeding, or operational difficulties affected the incidence of fainting. Menstruation was present at the relevant time in an equal number of fainters and non-fainters. Fainting was less common in the fortnight preceding menstruation than in the week after its cessation.

There was little difference between various occupational groups, and lack of food could have been a relevant factor only in a small proportion of the total number of faints. A high proportion of fainters gave a history of fainting either at a previous donation or on some other occasion. Among those who fainted, 13% lost consciousness, nearly 8% vomited, and 79% had only mild symptoms.

Returns from 4,212 donors who were asked to describe their feelings after bleeding showed that only 14% experienced some discomfort. Only 1.2% of men and 1.8% of women recorded delayed faints.

The conclusions reached are that: (i) there was no remediable factor except the exclusion of those with a known tendency to faint, (ii) the incidence of delayed faints was very small.

479

BLOOD VOLUME IN CHRONIC ANÆMIA BY A CONCENTRATED CORPUSCLE-HÆMOGLOBIN METHOD

by J. McMichael, E. P. Sharpey-Schafer, P. L. Mollison & J. M. Vaughan, *Lancet*, 1, 637-640, 22/5/43

This paper is by members of the Committee on Wound Shock and Blood Transfusion of the *Medical Research Council* and is based on work done at the *British Postgraduate Medical School* and at two of the four Blood Supply Depots which serve the London area.

It has long been known that in chronic anæmia the blood volume is below normal. In acute anæmia due to hæmorrhage the return of the blood volume to normal may also be prolonged. Methods of measuring the blood volume have not been widely used and are all open to certain criticisms on theoretical grounds. This comparison of three methods which can safely be used on seriously ill patients is therefore welcome.

The "concentrated corpuscle-hæmoglobin" method (CC-Hb) described by Hill in 1941 and the "concentrated corpuscle-differential agglutination" method (CC-DA) of Ashby (1925) both involve the administration of a blood

transfusion as part of the technique and are therefore particularly suitable for use with anæmic patients.

The former (CC-Hb) involves the transfusion of a known volume of blood, from which most of the plasma has been removed and which is therefore especially rich in erythrocytes. The hæmoglobin content of this blood, and also of the patient before and after the transfusion, is measured. A simple formula gives the patient's original blood volume, on the assumption that no gross displacements of plasma, either into or out of the circulation, occur during the transfusion.

The formula is

$$x = \frac{V(\text{Hb}_v - \text{Hb}_1)}{\text{Hb}_2 - \text{Hb}_1}$$

where x = patient's original blood volume

V = volume of blood transfused

Hb_v = hæmoglobin percentage of injected blood

Hb_1 = patient's Hb percentage before transfusion

Hb_2 = " " " after " "

Ashby's original CC-DA method has been modified by Mollison and others, and is said to be capable of giving results of the same order of accuracy as an ordinary erythrocyte count. It is only suitable for patients of blood groups A, B or AB. A known volume of blood from a group O donor is transfused. After the transfusion a sample of the patient's blood is taken and treated with an appropriate blood-grouping serum. This agglutinates the patient's cells but does not affect the group O cells of the donor. The agglutinated masses are removed by coarse filtration and the remaining cells are counted in the ordinary way. The blood volume at the end of the transfusion is given by the formula:

Final blood volume (cm^3)

$$= \frac{\left(\frac{\text{Volume of blood transfused}}{\text{Count of donor cells in patient's blood}} \right) \times \left(\frac{\text{erythrocyte count of transfused blood}}{\text{Count of donor cells in patient's blood}} \right)}{\text{Count of donor cells in patient's blood}}$$

Certain precautions needed in using this method are given in the papers already quoted.

The Evans-blue dye method of Gibson & Evans (1937) as modified by Harington, Pochin & Squire (1940) consists in giving an intravenous injection of 5 cm^3 of a 0.24 % solution of Evans-blue dye and then taking three samples of venous blood at half-hourly intervals. The concentration of dye in the serum is estimated colorimetrically and the plasma volume calculated by extrapolation backwards of the three points on the disappearance curve of the dye.

The results obtained by these methods are of great interest. Twenty-two cases were examined by the CC-Hb method, 2 of whom were suffering from various forms of chronic æmia and 10 from acute anæmia due to hæmorrhage. In 11 cases low blood volumes were found.

Five of these chronic cases and one of the acute cases were so examined by the CC-DA method and a very close correlation between the two estimates was obtained. In no case did the difference between the two methods exceed half a litre. In four cases the dye method was compared with the CC-Hb method and again good correlation was found.

A comparison of the low blood volumes recorded in the present series of cases of chronic anæmia and those published by Gibson indicate that the lowering is proportional to the severity of the anæmia.

Another interesting observation made in this series of patients was that the diastolic blood pressures were rather low but the systolic pressures were normal. This compensatory mechanism might be due to a marked reduction of the peripheral capacity of the circulatory bed. If this is the body's response to a low blood volume it might be desirable to produce the same effect by drugs in cases of surgical shock.

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THE DETERMINATION OF THE BLOOD VOLUME IN MAN WITH EVANS-BLUE ("T-1824")

by L. J. Davis, *Edinburgh Medical Journal*, 49, 465-483, August 1942

In the first part of this paper from the Department of Medicine, Edinburgh University, the various methods for the determination of the blood volume in man and the special advantages of the dye method are briefly considered. The author then discusses the various factors influencing the results obtained with the dye method, including choice of dye, mixing time and disappearance-rate of the dye, methods of estimation, hæmatocrit, and gives an excellent review of the relevant literature. He concludes that a spurious degree of accuracy is often attributed to existing methods of blood-volume determination, and that the evaluation of a blood-volume technique should be based upon its freedom from avoidable sources of error, its simplicity in operation, and the constancy with which comparatively accurate values can be obtained, rather than upon claims to a high degree of absolute accuracy involving tedious and time-consuming manipulations which may themselves introduce further errors.

In the second part of the paper the author describes the details of a simplified blood-volume technique, the results of which are presented. The technical procedure is essentially as follows: A sample of control blood is withdrawn from the patient and 5 cm^3 of a 240 mg. per 100 cm^3 solution of the blue azo dye "T-1824" are then injected through the same needle. Exactly 10 minutes later a test sample of blood is withdrawn from the opposite arm. Of this blood, some is mixed with anti-coagulant mixture for hæmatocrit determination and the remainder is allowed to clot. The concentration of the dye in the test-serum is subsequently estimated by means of the "spekker" photo-electric absorptiometer, serum from the control blood being used as a "blank." Details are given of a simple and reliable method of preparing a control dye-serum solution of known concentration for the purpose of checking the readings.

The results obtained with 11 normal male subjects are tabulated, the average total blood volume being 5,071 cm^3 , the volume per kilogram of body weight being 76.7 cm^3 , and per metre² of body surface 2,897 cm^3 . These results and their standard deviations are compared with those of 4 previous authors. In 5 of the patients the determinations were repeated and the differences between the pairs of readings were seen to be small (in no case more than 2.7 %).

The results of blood-volume determination in 10 patients suffering from pathological conditions are also given. These included 3 cases of severe anæmia and 5 cases of polycythæmia vera. In some of these cases the blood-volume determinations were repeated after appropriate treatment had been instituted. The findings accorded with those of previous investigators.

481

THE DETERMINATION OF PLASMA VOLUME BY THE EVANS-BLUE METHOD: The Analysis of Hæmolyzed Plasma

by C. J. O. R. Morris, *Journal of Physiology*, 102, 441-445, April 1944

The procedure developed in the London Hospital for the determination of plasma volume by the Evans-blue method has previously been described (Crooke & Morris, 1942). Even very slight hæmolysis in the samples of plasma may cause an error of about 5 % in the result since, during the extraction process, hæmoglobin is converted into a pigment (probably acid hæmatin) whose light absorption is in the same spectral region as that of Evans-blue. In conditions in which information about the plasma volume may be required it is not always possible to obtain specimens of plasma entirely free from hæmolysis, and a method was therefore sought in which this source of error could be eliminated. By an ingenious procedure, for details of which the original paper should be consulted, an optical method of correction for this error has been devised. The practical application of this method to plasma-volume determinations is described.

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BOOKS, MEMORANDA, REPORTS

[The prices quoted are those which obtain within the United Kingdom. Editors of medical journals who wish to review publications of which notices appear below are invited to apply to the Editor for review copies, of which a few are sometimes available. Orders for any of the publications mentioned below may be sent to BES Ltd., 6 Hanover Street, London, W. 1, England, if there are difficulties in obtaining them locally. Publications may be referred to by the numbers used below, preceded by the letters BMB, e.g. BMB 290/5. It should be noted that supplies of all publications are limited and there can be no certainty that publications ordered or requested for review will be available.]

482/66

OPERATIVE DENTAL SURGERY

by J. B. Parfitt & W. E. Herbert. Fifth edition. London, Edward Arnold & Co., 1944. 408 pages; 203 illustrations. £1 10s. [£1.5]

This book first appeared in 1921, being the substance of a course of lectures delivered at Guy's Hospital Dental School. Since that time successive editions have reflected the advances made in operative dentistry. Perhaps the most important recent development in prosthetic dentistry is the introduction of acrylic resins, both for dentures and restorative work, and the authors include a chapter dealing with its use in crowns, bridges and other restorations. The remainder of the book has been carefully revised and brought up to date; new illustrations and additional references have been included.

Chapter headings: (i) operative dentistry; (ii) infection and cleanliness; (iii) control of saliva; (iv) conservative treatment of parodontal disease; (v) ionic medication; (vi) the onset and growth of dental caries; (vii) treatment of dental caries; (viii) the teeth of children; (ix) conditions of permanence of tooth fillings, and general principles of cavity preparation; (x) pain-saving in the filling of teeth; (xi) the filling materials; (xii) filling teeth with gutta-percha; (xiii) dental cements and their uses; (xiv) the translucent cements; (xv) amalgam; (xvi) cohesive gold; (xvii) non-cohesive gold; (xviii) gold inlays; (xix) bridges; (xx) fused porcelain restorations; (xxi) pulpless teeth and their treatment; (xxii) the operation of crowning; (xxiii) acrylic resin restorations; (xxiv) the operation of extraction.

482/67

BROMPTON HOSPITAL REPORTS

Volume 12

London. Published by the Research Department of the Hospital, 1943. 163 pages. 8s. [£0.4]

This volume contains a collection of papers recently published from the Hospital. Dr. Margaret Macpherson¹ contributes an article on childhood infection and its relation to adolescent and adult pulmonary tuberculosis, in which she sums up the extensive work carried out by the research department of the Brompton Hospital during the past 14 years. A. Tudor Edwards² gives an authoritative survey of the modern treatment of traumatic hemothorax. There are two illustrated articles by C. Price Thomas and W. P. Cleland³ on the operation of thoracoplasty for pulmonary tuberculosis, which give a full account of the technique and results.

R. C. Brock⁴ describes the production of aseptic obliterative pleurisy by injecting silver nitrate into the pleural cavity. The same author, in another paper, discusses the treatment of tuberculous empyema and supplements his discussion with a most instructive analysis of the results of various therapeutic measures.

Other interesting papers in this volume include one by R. C. Wingfield on the control of tuberculous infection, and an original contribution by A. F. Foster-Carter⁵ on the anatomy of the bronchi.

¹ [see BMB 282] ² [see BMB 45] ³ [see BMB 266 & 267]
⁴ [see BMB 44] ⁵ [see also BMB 245 & 246]

482/68

INDUSTRIAL MEDICINE

edited by Sir Humphry Rolleston & Alan A. Moncrieff. London, Eyre & Spottiswoode (Publishers) Ltd., 1944. 202 pages. 16s. [£0.8]

Eleven of the 18 contributions comprising this symposium on industrial medicine have been specially written for it; the remainder were first published in the *Practitioner*, December 1942, and have been revised before republication.

The war has brought about a huge increase in the number of persons engaged in industry, and this has led inevitably to an increase in the incidence of disease directly attributable to industrial causes. By the foresight of the Minister of Labour, provision was made in 1940 for the employment of whole-time medical officers and nurses in factories large enough to warrant them; part-time medical officers are employed in smaller establishments. This closer association of the practitioner with the factory is certain to continue after the war, and such contact with "occupational medicine" on the part of the general practitioner will inevitably benefit both the employer and the employee.

This symposium will serve as an excellent introduction for the general practitioner desiring to acquaint himself with the commoner industrial diseases and with problems of general hygiene and administration. It contains the following contributions: (i) introduction: industrial medicine and the general practitioner (Sir David Munro); (ii) industrial poisons (H. M. Vernon); (iii) industrial dermatoses; diagnosis and treatment (A. D. K. Peters); (iv) chest disease in industry (A. J. Amor); (v) miners' nystagmus

(W. J. W. Ferguson); (vi) toxic anæmia (Ethel Browning); (vii) the treatment of the injured workman (W. Gissane); (viii) back-strain (F. W. Holdsworth); (ix) neuroses in industry (E. H. Capel); (x) malingering (D. C. Norris); (xi) nutritional problems related to industrial workers (H. A. Krebs); (xii) adolescents in industry (Sir Henry Bashford); (xiii) fatigue and boredom (May Smith); (xiv) lighting problems (E. W. Murray); (xv) ventilation and heating (T. Bedford); (xvi) welfare services (R. R. Hyde); (xvii) the works ambulance room (P. Pringle); (xviii) factory law in relation to health and welfare (A. I. G. McLaughlin).

482/69

VARICOSE VEINS, HÆMORRHOIDS, AND OTHER CONDITIONS

Their Treatment by Injection

by R. Rowden Foote. London, H. K. Lewis & Co. Ltd., 1944. 119 pages; 54 illustrations. 12s. 6d. [£0.625]

At the time of its introduction, the injection treatment of varicose veins was welcomed as a useful new method of alleviating this condition, but sufficient data have now been published to show that a high recurrence rate must be expected. This finding has led many to abandon injection therapy in favour of conservative treatment or high ligation. The author of this monograph, who is physician in charge of the Injection Clinic, Royal Waterloo Hospital, considers that too many cases are at present treated operatively, and that many require treatment by injection only. He discusses both aspects of this question and gives a full account of the ætiology of varicose veins and of their treatment by injection and operation. In addition, the injection treatment of hæmorrhoids, hydrocele, hernia and other conditions is described. This book, which is well illustrated, provides a good picture of injection therapy at the present time.

482/70

* RECENT ADVANCES IN ANÆSTHESIA AND ANALGESIA

(Including Oxygen Therapy)

by C. Langton Hewer. 5th edition. London, J. & A. Churchill, 1944. 343 pages; 141 illustrations. 18s. [£0.9]

A new volume or new edition in the *Recent Advances* series, to which this book is an outstanding contribution, is almost always an event of some importance. Although the fourth edition appeared in 1943, sufficient new work has been reported to make possible this new edition. Besides an account of modern anæsthesia and analgesia, it gives new information on anæsthesia for thyrectomy, general analgesia with ethyl chloride and trichlorethylene, intravenous general analgesia with procaine, improved apparatus for controlled respiration, pethidine analgesia in obstetrics, pressure infiltrators, fractional caudal block, suction from oxygen cylinders, etc. There is an additional chapter on anæsthetic charts and records. Each chapter includes a useful list of references for further reading; there is room for improvement in the method of presentation of these references.

Chapter headings: (i) theoretical aspects of inhalational anæsthesia; (ii) premedication; (iii) nitrous oxide and the hydrocarbon gases; (iv) carbon dioxide and helium; (v) modern apparatus for the administration of the "gas" anæsthetics; (vi) recent work on the ethers; (vii) the halogen-containing anæsthetics; (viii) recent developments in endotracheal anæsthesia; (ix) the explosion risk in anæsthesia; (x) intravenous anæsthesia and analgesia; (xi) general aspects of local analgesia; (xii) drugs used in local analgesia; (xiii) recent advances in the technique of local analgesia; (xiv) the present position of spinal analgesia; (xv) collapse and resuscitation; (xvi) anæsthesia and analgesia for neuro-surgery; (xvii) anæsthesia and analgesia for dental surgery; (xviii) anæsthesia and analgesia for endoscopy, for nasal and oral surgery, for war wounds involving the mouth, and for operations upon the pharynx and larynx; use of suction; (xix) anæsthesia and analgesia for thyroid and thymic surgery; (xx) anæsthesia and analgesia for thoracic surgery; (xxi) anæsthesia and analgesia for abdominal surgery; (xxii) anæsthesia and analgesia in obstetrics—resuscitation of the new-born; (xxiii) anæsthetic sequelæ; (xxiv) psychological aspects of anæsthesia and analgesia; (xxv) oxygen therapy; (xxvi) anæsthetic charts and records.

482/71

ECONOMY IN THE USE OF DRUGS IN WAR-TIME

Medical Research Council War Memorandum No. 3. Revised second edition. With an Appendix on Economy in the Use of Bactericides. London, H.M. Stationery Office, 1944. 16 pages. 3d. [£0.0125]

The first edition of this Memorandum, issued in March 1941, expressed the considered opinions of the Therapeutic Requirements

Committee, which was appointed in September 1939 by the *Medical Research Council* in consultation with the Ministry of Health. The object of the publication was to give to those concerned with the supply of drugs an indication of the relative therapeutic importance of the drugs in ordinary use, and to members of the medical profession some information regarding the availability in war-time of the materials which they were accustomed to prescribe.

In preparing the first edition, the scope was extended, after consultation with the Ministry of Agriculture and Fisheries, to include veterinary applications of drugs.

In November 1941 the First Supplement to this Memorandum was issued, in order to bring the recommendations up to date. In April 1942 a Memorandum on Economy in the Use of Bactericides, prepared by the Therapeutic Requirements Committee, was issued by the *Medical Research Council* to the medical and pharmaceutical press.

Since the publication of the first edition of the present Memorandum, effect has been given to its recommendations, by means of Addenda to the *British Pharmacopæia* 1932, Supplements to the *British Pharmaceutical Codex*, and the *National War Formulary*. A new edition is now considered advisable, in consequence of changes in the supply position of many drugs, the introduction of new remedies, and increased knowledge of drugs as the result of war-time experience.

482/72

REGIONAL ANALGESIA

by H. W. L. Molesworth. London, H. K. Lewis & Co. Ltd., 1944. 90 pages; 42 illustrations. 8s. 6d. [£0.425]

The author of this book has had much experience in the use of regional analgesia, and he discusses fully the advantages and disadvantages, the indications and contra-indications for this form of anaesthesia. While not to be regarded as a textbook on the subject, this little volume contains much practical information and many useful illustrations.

Chapter headings: (i) general principles; (ii) methods of regional analgesia; (iii) the upper extremity; (iv) the lower extremity; (v) the head and neck; (vi) the thorax; (vii) the abdomen; (viii) spinal analgesia.

482/73

REPORT OF INTER-DEPARTMENTAL COMMITTEE ON MEDICAL SCHOOLS

published by the Ministry of Health and the Department of Health for Scotland. London, H.M. Stationery Office, 1944. 312 pages. 4s. 6d. [£0.225]

To meet the requirements of the proposed National Health Service, fundamental changes will be necessary in the methods of recruitment and training of future doctors. This was foreseen by the appointment of the Inter-departmental Committee on Medical Schools, under the chairmanship of Sir William Goodenough. The Ministry of Health and the Department of Health for Scotland have now published the findings of this committee (the "Goodenough Report").

The principal recommendations of the committee are: (i) drastic overhaul of undergraduate training: more attention to be paid to social medicine, the promotion of health, and the prevention—as well as cure—of disease, to children's health and to mental health; (ii) co-education in all medical schools, and sex equality in hospital appointments; (iii) greatly increased Exchequer grants for medical education and research, and more financial help for students; (iv) reform of examination system; (v) compulsory hospital appointments after qualification and before entry into independent practice; (vi) changes in the policies and organization of medical schools and teaching hospitals; more whole-time teachers, and salaries for part-time teachers; (vii) a comprehensive system for the training of specialists; (viii) development in London of a world centre for post-graduate medical education and research; (ix) linking of all major hospitals with teaching centres.

The proposed changes will take some time to become fully effective. An increased number of teachers and additional accommodation and equipment will be necessary. The training of students can be conducted only under the ægis of a university and in institutions that conform to university standards. For this reason the committee suggests the abolition of 4 medical schools which it feels cannot adequately meet the needs of modern medical education. The unit of organization for undergraduate medical education should be a medical teaching centre consisting of a university medical school with a group of teaching hospitals in as close proximity as possible to it, and such clinics of the health service of the district as should be used for teaching purposes. While the governing body of each constituent of a teaching centre should retain full authority in its own field of responsibility, the policy, administration and activities of each institution should be so interrelated with the other constituents as to provide a single unit in the field of medical education and research.

More whole-time appointments to the teaching staff and the payment of salaries to clinical teachers are among changes proposed.

At present there is great inequality in the distribution of medical schools, with a maximum concentration in central London. It is suggested that *Charing Cross*, *St. George's*, *Middlesex*, and the *Royal Free* hospitals (and their respective medical schools) should all consider moving to sites further from the centre of London. As far as the establishment of new medical schools is concerned, the committee concludes that "the financial resources and the suitably qualified teachers likely to be available will be wholly needed for a long time for the development of existing schools to their full capacity."

Before the establishment of a new school "there must first be proof of a national need for another school. . . . The aim should be to secure better facilities for the existing schools and to improve and develop the exceptional facilities of London for post-graduate medical education."

The kind of post-graduate training and experience required by intending specialists and the means whereby it can be obtained have been examined by the committee as questions of great importance, both in the operation of the health service and in the sphere of medical education. On the assumption that the qualifications and standards of specialists are determined by some central machinery and that the primary requisite will be approved post-graduate training and experience extending over not less than 4-5 years after registration, the committee makes various suggestions, including the following: (i) that, while holding hospital appointments, the intending specialist should be regarded as a trainee and be given adequate time for reading, reflection and research; he must not be over-burdened with routine work and he must be adequately remunerated; (ii) usually, before he begins to specialize, he should have at least six months' resident clinical experience of general medicine or surgery; (iii) every trainee should have the opportunity to devote himself for a period to the extension of his scientific knowledge by laboratory work and study, and provision should be made, by such means as travelling fellowships for trainees, to obtain the benefit of working for a time in suitable hospitals and medical schools abroad. Post-graduate study should be a regular and recognized feature of general practice.

A scheme is outlined for the development of the exceptional resources of London for the post-graduate education of medical practitioners from all parts of the world. This scheme involves the reconstitution of the *British Postgraduate Medical School* on a federal basis embracing a comprehensive range of post-graduate institutes in all branches of medicine.

Young research workers should mainly recruit themselves; and when a research worker has proved his ability and has chosen research as a career, he should be given reasonable security in this career. Public grants to medical schools and teaching hospitals must include basic research grants; extra grants will also be needed for the support of special investigations.

One of the most important recommendations is that each student, after passing his qualifying examination, shall complete a 12 months' period of hospital appointments before being admitted to the Medical Register and allowed to enter independent practice.

In the past, insufficient attention has been paid to social medicine. "A new orientation of medical education, a big expansion of the social work of teaching hospitals and radical changes in the outlook and methods of most of the teachers" are necessary if students are to be fitted to become health advisers and members of a national health service. Improvements are also necessary in the teaching of child-welfare work, and "in many schools the experience which students gain of maternity work falls far short of what is necessary." Training in psychiatry, also, has failed to keep pace with the growing realization of the important place which the subject should occupy; an adequate department of psychiatry is essential in each medical centre.

"Unsuitability for a medical career should be the sole barrier to admission to a medical school." Co-education has proved successful in all medical schools outside London and it should become the practice in every medical school. It is recommended that the payment to any school of a government grant should be conditional upon the school admitting a reasonable proportion of women students; all hospital appointments of qualified practitioners should be filled by open competition and sex should not be a bar to appointment. Grants to medical students should compare more favourably than at present with grants to students in other faculties. Such grants should be adequate in amount and should extend over the whole of the period of training. Arrangements for scholarships and grants need simplification, and medical schools should have larger funds at their disposal to help students and to encourage recruits.

It is estimated that the supply of doctors necessary in civilian practice in Britain is within the capacity of existing schools provided that those schools which are below an economic size are expanded; it is considered that a school of normal size is one able to admit 100 students a year.

The committee estimates that, including the outlay of teaching hospitals on facilities for teaching and research, the total of capital expenditure that should be incurred may, within ten years, amount to £10,000,000 at pre-war costs. In addition, the amount of recurrent grants will have to be increased yearly from £700,000 a year, the approximate amount before the war, until within ten years the amount reaches between £3,000,000 and £4,000,000 a year at pre-war values. At this level recurrent grants would represent about 2% of the estimated cost in the first year of the National Health Service.

The report, which is unanimous, is signed by Sir William Goodenough, Sir John Stopford, Professor T. R. Elliott, Dr. A. M. H. Gray, Professor J. Hendry, Professor A. V. Hill, Sir Wilson Jameson, Professor J. R. Learmonth, Sir Ernest Pooley and Dr. Janet Vaughan.

482/74

COMMON SKIN DISEASES

by A. C. Roxburgh. Seventh edition. London, H. K. Lewis & Co., Ltd., 1944. 454 pages; 192 illustrations. 18s. [£0.9]

Seven editions of this book have appeared in 12 years, and this latest edition maintains the high standard, both of text and illustrations, set by its predecessors. The book gives a short account of the common dermatoses and their treatment. The most important changes made in the new edition are in the section on

industrial dermatitis, which has been expanded on account of its increasing prevalence, and in the chapter on the avitaminoses, which has been rewritten. The section on scabies takes account of the important work done on this condition since the war. Two addenda deal with (i) immersion foot, a condition which has become increasingly prevalent during the last few years and one on which much has been written; and (ii) the results of the use of penicillin in dermatology. The author has already recorded his experiences with penicillin and considers that it will prove of especial value in the treatment of certain staphylococcal and streptococcal infections of the skin and in the control of sycosis.

Chapter headings: (i) general aetiology and pathology; (ii) signs, symptoms and general diagnosis; (iii) general treatment; (iv) congenital affections of the skin; (v) skin affections due to physical causes; (vi) dermatitis due to chemical causes; (vii) drug eruptions; (viii) diseases due to animal parasites; (ix) diseases due to vegetable parasites; (x) diseases due to filterable viruses; (xi) syphilis; (xii) diseases due to obstruction of vessels; (xiii) neurodermatoses; (xiv) toxic eruptions; (xv) eczema, Besnier's prurigo, cheiropompholyx; (xvi) psoriasis and pityriasis rubra; (xvii) lichen planus; (xviii) diseases of hair and nails; (xix) diseases of sebaceous and sweat glands; (xx) tumours; (xxi) atrophy and sclerosis; (xxii) vesicular and bullous eruptions; (xxiii) the erythrodermias; (xxiv) avitaminoses.

482/75

REPORT ON THE INCIDENCE OF RICKETS IN WAR-TIME

by the British Paediatric Association. Ministry of Health: Reports on Public Health and Medical Subjects, No. 92. London, H.M. Stationery Office, 1944. 36 pages. 9d. [£0.0375]

At the invitation and with the co-operation of the Ministry of Health, the British Paediatric Association undertook a combined clinical and radiological examination of 5,283 children between the ages of 3 months and 18 months in 23 centres in Britain, to ascertain whether or not there was any war-time change in the incidence of rickets. Positive radiological evidence of rickets was reported in 106; from these figures it is shown that the rate of incidence of rickets diagnosed radiologically was 2½% before 6 months of age, 4% during the first year of life, and negligible over this age.

The clinical diagnosis of the condition varied in different areas from nil to 61%; only a small proportion of clinically positive cases was confirmed radiologically. Most observers agree that severe rickets with deforming bone changes has almost disappeared from Britain, and with this disappearance the clinical conception of rickets must undergo some modification. A disturbance of calcification demonstrable radiologically but not clinically may need a new terminology. Among radiologically negative children 81½% were breast fed, whilst among radiologically positive children 69% were breast fed. These findings confirm the fact that breast feeding alone, although important in the prevention of morbidity and mortality, cannot be relied upon to prevent the occurrence of rickets. Nevertheless, rickets is more likely to appear in artificially-fed than in breast-fed babies.

It is shown that, of children free from rickets on radiological examination, 85½% had received cod-liver oil or other vitamin D preparation, whereas the figure for the radiologically positive children was only 73%.

The report concludes that comparison with previous surveys affords no evidence of any war-time increase in radiological rickets. Nevertheless, certain cases in the groups examined did show an incidence which still gives scope for better prophylactic measures, of which the Government's national "cod-liver oil" compound is an important one. The report calls attention to the difficulties associated with the early diagnosis of rickets and the present-day position of the nutritional problem of adequate calcification of bone in the active growing child.

482/76

DEPARTMENT OF HEALTH FOR SCOTLAND

Summary Report for the Year ended 30th June, 1944

Edinburgh, H.M. Stationery Office, 1944. 23 pages. 4d. [£0.016]

This report shows that, in spite of war-time conditions, the general standard of health in Scotland is being maintained. Although there is a slight rise in the infant mortality rate, the still-birth and maternal mortality rates are the lowest yet recorded. Notifications of new case of pulmonary tuberculosis continued to increase, and are now more than 50% above the figure for 1938; this may be due in some measure to mass miniature radiography and other improved diagnostic facilities.

Among infectious diseases there was a small decrease in venereal disease, although the number of new cases continues to cause concern. There is a striking decrease in the figures for diphtheria, no doubt due to immunization of the child population. Recently there has been a tendency for the proportion of immunized children to fall, and it is proposed to launch another campaign to encourage immunization.

The health of school children is being maintained and, in some instances, improved. The Miners' Centre established in 1943 for the rehabilitation of disabled miners has already demonstrated its value. Progress is reported in the development of plans for post-war health services and for an attack on the serious problems of unsatisfactory housing.

The authorities realize that the successful operation of modern measures for improving the health of the nation depend on the co-operation of individual citizens; for this reason the Scottish Council for Health Education, constituted in 1943, must in time be of great value in promoting and encouraging health education.

482/77

A STUDY OF VARIATIONS IN OUTPUT

by S. Wyatt (assisted by R. Marriott, W. M. Dawson, D. E. R. Hughes & F. G. L. Stock). Emergency Report No. 5 of the Industrial Health Research Board, Medical Research Council. London, H.M. Stationery Office, 1944. 16 pages. 4d. [£0.016]

Investigations were made on representative groups of about 200 workers in each of several factories engaged on war production, with a view to ascertaining the effect of a reduction in working hours upon output. The reduction was small (from about 54 to 51 hours per week) but this relaxation of working time was followed by an increase of 3% in the output per hour during the first and second four-week periods after the change, rising to 6% in the next four weeks. The general trend was for weekly output to be higher with the shorter working day. Changes in output often depended, however, on other factors than the effect of shorter hours, i.e. changes in the type or design of product, mechanical difficulties and machine breakdowns, variations in quantity and quality of the material used, working conditions, changes in type and layout of machines.

While it is shown that a shortened working week may be expected to be followed by increased output and decreased absenteeism, changes in the design of machines, of the lay-out of work and of the form or type of product are particularly important factors influencing output. "Machines should be made for men: not men forcibly adapted to machines. Such alterations of design, to produce all round favourable effects, must be so shaped that the demand on the individual worker does not diverge significantly from what may be reasonably expected from the average abilities of the working group."

482/78

THE TRAINING OF THE NURSERY NURSE

Interim Report of the National Council for Maternity and Child Welfare published by the National Society of Children's Nurseries, 117 Piccadilly, London, W. 1. 19 pages

At the request of the National Council for Maternity and Child Welfare, a group committee was formed by the National Society of Children's Nurseries to report on the training of nursery nurses. The interim report of this committee includes the following recommendations: (i) prospects and conditions of service for nursery nurse students should be set out and made public, and the co-operation of headmistresses should be secured to ensure the enlistment of suitable candidates; (ii) the minimum age of admission for nursery training should be 16; (iii) candidates should have received a secondary-school education or provision should be made for suitable elementary school-girl candidates to receive further general education; (iv) periodical medical examination and careful watch and record of the nursery student's health is essential; (v) the maximum hours of work should be 96 a fortnight with a minimum of 4 weeks' holiday per annum; (vi) adequate recreational facilities should be provided; (vii) the training course should be for 2 years, including a 3 months' probationary period; (viii) the curriculum should cover an elementary study of everything concerned with the physical and mental development of the child, together with simple ailments and first aid, and instruction in domestic subjects; (ix) in addition to the training staff working in the nursery, the services of specialist lecturers (doctors, health visitors, child psychologists, etc.) should be available; (x) nurseries wishing to give training should be subject to initial and periodic inspection by properly qualified inspectors. The report also recommends that all students should be required to sit for both practical and theoretical examinations and that there should be one national examining board to award a diploma to successful candidates; such a diploma should qualify for the post of (a) staff nurse in a nursery, (b) children's nurse in private households, and it should be considered as a basis for further training for higher posts in children's nurseries, hospital nursing, nursery school teaching, social welfare work, etc.

482/79

VITAL STATISTICS IN THE TROPICS

by P. Granville Edge. Foreword by M. Greenwood. London, Baillière, Tindall & Cox, 1944. 188 pages. 12s. 6d. [£0.625]

"Thus Dr. B. has, for our instruction, imitated on a small scale the vast experiment which is constantly going on, and destroys thousands of men, women and children all over England. . . . More than two millions of people live in London over sewers and cesspools. . . . Will the London Beards of life in London ever experiment? Are they, like Dr. B., convinced and satisfied? Works stop their common sense to bear on this question? . . . The sweet Will they bring their common sense to bear on this question? . . . The admirable that enter the country are taxed; and every one has witnessed the odours of Her Majesty's customs' officers in their search for Eau de Cologne. If a tax could be levied upon the odours of another description, bearing some proportion to the evil they do, it would be much more productive."

Statisticians excepted, few people would accept the view that statistical literature is ever light, easy and interesting reading. And even amongst statisticians of the modern schools, few would guess correctly the source of the above quotation to be the annual reports of the Registrar-General for England and Wales. Yet it will be found on pp. xix and xx of his report for 1855 and, selected at random by the reviewer, typifies the style of many of the reports in the period 1856 to 1875. The present-day civil servant, circumscribed by sub-committees appointed by committees of the Joint Conferences on this and that, would find some difficulty in obtaining sanction for publication, if he presented his report in such terms as those quoted. Nowadays, partly owing to the growth of a specialised technique, statistical reports have acquired a language

of their own, and couched in stereotyped and cautious terms, are not easy reading for the man in the street.

From the point of view of both popular and statistical appeal Major Edge is fortunate in his subject, in that he deals with peoples and places far more primitive than was our own land at the time when Registrar-General Graham was advocating the abolition of London cesspools as a means of lowering the prevailing high mortality rates. The only thing uninteresting about his book is the title. It would better have been termed "The romance of the tropics as expressed in vital statistics."

The general arrangement is readily appreciated. Under every heading—numbering of the population, systems of birth and death registration, or the collection of other statistical information—the author discusses first, methods in countries which have had long experience of such systems. Their evolution is briefly traced, and the uses to which the information demanded of the citizen is put, for his own advantage, are clearly demonstrated. From this aspect alone, the book may well be read not only by colonial medical officers of health for whom it is obviously primarily intended, but also by the general public, who will be cheered to find that the numerous forms they fill in, often have a definite advantage for mankind.

Next he demonstrates the futility of attempting to impose the same methods of census-taking and registration on indigenous populations, and the fallacies which may appear in the results of these methods are persisted in against native prejudices. It is in so doing that he takes the reader with him to the less trod corners of the earth—Borneo, Malaya, Nigeria, the Andaman Isles—to name only four—and presents the collection of vital statistics more in the guise of books on travel. Of the difficulties of obtaining records of plural births he writes:

"The Wabugwe tribe of Tanganyika also believed in the ill luck surrounding twins, and were accustomed to expose such infants to die in the bush. But curiously enough, a neighbouring tribe, the Wambulu, had no such prejudices, and as the birth rate of this tribe was low, they would freely adopt abandoned children; so the custom had developed under which Wabugwe twins would be exposed on the borders of the Wambulu territory, where they were taken by this tribe and brought up as their own."

In addition he supplies constructive suggestions as to how these many difficulties, by studying native customs, may be to some extent overcome. For example:

"In the post-natal period curious customs and practices are sufficient in number and variety to remind the observant stranger of the presence in the community of newly-born children. These evidences are seen in the food *tabus* of nursing mothers, the wearing of special abdominal bandages, and special ornaments, the smearing of bodies with earth, oil, etc. and the special signs of recent motherhood which provide exemption from tribal duties involving heavy labour."

Entertained so hugely, the reader will be in the mood merely to smile at certain inconsistencies as evidencing the author's enthusiasm. Throughout each chapter he stresses the importance of proceeding slowly in the introduction of new schemes of registration, and the care needed to avoid arousing the resentment of the natives by demanding information relating to their tribal life. Yet he suggests:

wherever possible some or all of the following facts should be recorded whenever the birth of a child is registered—race, tribe, colour, age at marriage, duration of marriage, occupation, religion, number of children (a) born alive and living (b) born alive but dead, (c) still-born; and whether the newly-born child was the mother's first-born, or otherwise (2nd, 3rd etc.)."

When it is remembered that although birth registration has been compulsory in England for over a century, figures relating to still-births have been available only since 1931; and that it was only in the face of a good deal of resentment by the natives of England that it was made compulsory in 1939 to supply information regarding the age of the mother and the number of previous children when registering a birth, the anomaly is striking.

A foreword by Professor Major Greenwood praises the book, and may be of use in correcting any impression some readers may form that the collection and tabulation of data and the calculation of simple birth and death rates are all that is needed in the compilation of a statistical report.

482/80

THE SURGERY OF ABDOMINAL TRAUMA

by Geoffrey E. Parker. London, J. & A. Churchill Ltd., 1944. 120 pages; 10 illustrations. 10s. 6d. [£0.525]

The reports of 94 cases of abdominal and abdomino-thoracic wounds seen and treated by the author during the Italian and Tunisian campaigns form the basis of this work. As the preface points out, problems are encountered on the battlefield which, apart from accidents on the road and in the factory, are without parallel in peace-time surgery. The book has therefore been written to assist surgeons who, although experienced in general surgery, are about to undertake military surgical work, and also for those practising surgery in industrial areas. The author does not consider that there is such a thing as the clinical diagnosis of an "absolutely hopeless abdominal injury"; such cases should always be given the chance that operation provides. He also stresses the view, widely held, that the time interval from wounding until the patient stops moving must be cut down to a minimum by taking the surgeon as near to the line as possible; the period required for rest, resuscitation, etc., before the optimum level is reached, varies between half an hour and six hours or longer. The quicker the patient is brought to the operability level, the better his chances of survival.

This is a useful little book, worthy of the attention of surgeons serving with the Armed Forces. Chapter headings: (i) diagnosis of abdominal injury; (ii) pre-operative treatment and resuscitation; (iii) general operative considerations; (iv) technique of the repair of abdominal viscera; (v) statistics; (vi) case notes; (vii) post-operative treatment and its principles.

482/81

NOTABLE NAMES IN MEDICINE AND SURGERY

by Hamilton Bailey & W. J. Bishop. London, H. K. Lewis & Co. Ltd., 1944. 202 pages; 142 illustrations. 15s. [£0.75]

For those who prefer to take their history of medicine in small doses, this is an admirable book, as valuable to nurses and other medical auxiliaries as to doctors themselves. There is something interesting on every page. Several thousand proper names exist in medical terminology, and while we are familiar with "Unna's paste" and "Koplik's spots," with "Ménière's disease" and "Trendelenburg's position," few of us know much about the men who have been thus eponymized. A well-known surgeon has collaborated with the sub-librarian of the Royal Society of Medicine in the production of the book, which consists of brief sketches of the lives and work of 83 men and women who have made notable contributions to medicine and whose names are perpetuated in medical terminology. A portrait is included with each sketch and the book is interspersed with many other interesting illustrations. The book will serve as an excellent stimulant to a further interest in the study of the history of medicine.

482/82

MODERN TREATMENT YEAR BOOK 1944

A Year Book of Diagnosis and Treatment for the General Practitioner edited by C. P. G. Wakeley. London, Medical Press & Circular, 1944. 300 pages; 17 plates, 15 illustrations. 15s. [£0.75]

This volume, the tenth in the series, comprises 42 articles, contributed by well-known authorities in Britain. The first 21 articles deal with a variety of subjects in medicine, surgery, gynaecology and obstetrics, while the remaining contributions discuss modern methods of treatment of diseases and injuries associated with war. The aim of this volume is to provide a concise account of recent progress in treatment and it is especially suitable for the doctor in the Armed Forces and the busy general practitioner.

483

GUIDE TO THE JOURNALS

Archives of Disease in Childhood

19 : June 1944

The incidence of rickets in war-time. (British Paediatric Association) 43-67
The incidence of rickets in children attending hospitals in Bristol, from September 1938 to May 1941. (B. D. Corner) 68-86
Observations on tuberculous meningitis. (J. McMurray) 87-92
An analysis of the fate of premature babies in Warwickshire for 1942 and 1943. (C. F. Brockington) 93-95

Biochemical Journal

38 : 1944

PARTIAL INDEX

Iodometric and colorimetric methods for the estimation of calcium in serum based on the use of an improved permanganate solution. (J. A. de Loureiro & G. J. Janz) 16-19
Human-milk fat. I. Component fatty acids. (T. P. Hilditch & M. L. Meara) 29-34
The 'cyclization' of vitamin A and allied compounds. (E. G. E. Hawkins & R. F. Hunter) 34-37
Tissue nucleic acids. I. Ribonucleic acids and nucleotides in embryonic and adult tissue. (J. N. Davidson & C. Waymouth) 39-50

The 'activation' of phosphatase. (G. E. Delory & E. J. King) 50-53
Serum gonadotrophin. 2. Further purification of the active material. (C. Rimington & I. W. Rowlands) 54-60
A method for the assay of penicillin. (N. G. Heatley) 61-65
The metabolism of 2:4:6-trinitrotoluene (a T.N.T.). (H. J. Channon, G. T. Mills & R. T. Williams) 70-85
Studies on cholinesterase. 4. Purification of pseudo-cholinesterase from horse serum. (F. Strelitz) 86-88
The analysis of hair keratin. 2. The dicarboxylic and basic amino-acids of human hair. 3. Isolation of proline from human hair. (J. M. R. Beveridge & C. C. Lucas) 88-97
Biochemical characterization of the actions of chemotherapeutic agents. 1. Measurement of growth of streptococcal cultures through their gaseous metabolism, and the effects of pantothenate and pantoyletaurine upon the metabolism and growth. (H. McIlwain) 97-105
Synthesis of vitamin C in stored apples. (C. West & S. S. Zilva) 105-108
Metabolism of steroids. 4. Ketonic acids derived from cholic acid. (G. A. D. Haslewood) 108-111
A growth factor for *C. diphtheriae* present in liver. (F. W. Chattaway, F. C. Hapgood & M. Sandford) 111-115
A new coupling component and simplified method for the estimation of sulphanilamide drugs. (F. L. Rose & H. G. L. Bevan) 116
Experiments on the practicability of increasing calcium absorption with protein derivatives. (T. C. Hall & H. Lehmann) 117-119
The metabolism of lysine. (A. Neuberger & F. Sanger) 119-125
The availability of ϵ -acetyl-*D*-lysine and ϵ -methyl-*D*-lysine for growth. (A. Neuberger & F. Sanger) 125-129

- The reticulosos. (W. N. Goldsmith) 107-128
Lymphadenoma: its aetiology, and its skin lesions. (E. C. Warner) 129-135

British Journal of Experimental Pathology

25 : April 1944

- Observations on the bactericidal and bacteriostatic actions of *p*-aminobenzene-sulphonamide and *p*-hydroxylaminobenzenesulphonamide, with special reference to their suppression by *p*-aminobenzoic acid. (J. W. McLeod, A. Mayr-Harting & N. Walker) 27-37
The effect of cell growth-promoting tissue extracts on the healing of experimental cutaneous wounds in rats. I. Local application. (E. Auerbach & L. Doljanski) 38-45
Effects of South Wales anthracite coal and of precipitated amorphous silica upon the lungs of mice. (J. A. Campbell) 46-55
Experiments on the inhibitor occurring in Rous No. 1 sarcomas. (J. G. Carr) 56-62
The action of sulphonamides against *Treponema recurrentis*. (F. Hawking) 63-67
The liberation of virus, together with materials that inhibit its precipitation with antiserum, from the solid leaf residues of tomato plants suffering from bushy stunt. (F. C. Bawden & N. W. Pirie) 68-80

British Journal of Ophthalmology

28 : August 1944

- The value of penicillin in the treatment of superficial infections of the eyes and lid margins. (T. Crawford & E. F. King) 373-383
The incidence of eye disease in the Australian Imperial Forces, Middle East. (J. B. Hamilton) 383-393
Ocular neurosis. (A. M. G. Campbell & A. G. Cross) 394-402
Operations on one hundred cases of convergent concomitant squint. (S. H. Faulkner, E. Scully & E. E. Carter) 403-407
A simplified external dacryocystorhinostomy. (J. L. D. Williams & B. G. Hill) 407-410
A case of corpora nigra with anterior synechia. (R. Crawford) 410-412
Unilateral membranous conjunctivitis, with complete cast. (J. F. Galpine & D. R. Campbell) 412-414

British Journal of Radiology

17 : August 1944

- Team work in the treatment of cancer. (H. S. Souttar) 229-234
The volume localisation of deep-seated tumours by means of tomography. (E. M. Ungar, G. Spiegler & D. W. Smithers) 235-238
Radiographic abnormalities of stomach and colon in mental defectives. (W. E. Snell) 239-240
The future of radiology in obstetrics. (J. B. Hartley) 241-246
Some observations on dental changes in possible riboflavin deficiency. (J. A. Ross) 247
The calculation of dosage rate in rectangular fields. (F. Bush) 248-250
Radiological observations and the description of a cardiac pouch in carcinoma of the cardiac end of the stomach. (A. Elkeles) 251-254
Further notes on the structure and function of the intervertebral disc. (G. Doel) 255-256
"Stress" fracture of bone. (D. R. Bertram) 257-258
Precise pelvimetry. (W. H. Hastings) 259-260

17 : September 1944

- Sylvanus Thompson Memorial Lecture. (S. Russ) 261-264
Some problems of appendix radiology. (A. M. Rackow) 265-270
The effect of ionizing radiations on the broad bean root. Part VI. (L. H. Gray & J. Read) 271-273
A particular type of tuberculous pulmonary cavitation tending to heal spontaneously. (L. Dunner) 274-277
Air absorption corrections for soft X rays. (C. E. Eddy & J. L. Farrant) 278-279
Radiological estimation of splenic enlargement in malignant tertian malaria. (W. H. T. Shepherd) 280-285
The importance of air encephalography in investigation of epilepsy of late onset. (J. McM. Mennell & C. Worster-Drought) 286-288

British Journal of Tuberculosis and Diseases of the Chest

38 : April & July 1944

- Pulmonary hydatid disease. (N. R. Barrett & D. Thomas) 37-95

British Medical Journal

2 : 29/7/44

- Localization in the cerebrum and cerebellum. (E. D. Adrian) 137-140
Some problems in riboflavin and allied deficiencies. (H. S. Stannus) 140-144
Post-operative strain in the Navy. (D. Curran & G. Garmany) 144-146
Schick reactions in recently confined women and their infants. (G. P. Wright & W. M. Clark) 146-148
Radiotherapy of ectopic calcification. (E. Millington) 148-149
Some common paediatric procedures: a reassessment for child welfare practice. (D. Bell) 157-158

2 : 5/8/44

- Penicillin: a survey. (H. W. Florey) 169-171
Treatment of acute empyema with penicillin. (E. C. B. Butler, K. M. A. Perry & F. C. O. Valentine) 171-175
Penicillin in ophthalmology. (J. G. Milner) 175-178
Penicillin and sulphonamides in infantile gastro-enteritis. (E. Burns & W. Gunn) 178-180
A severe haemolytic transfusion reaction due to the Rh factor. (A. Beck, C. V. Harrison & J. M. Owen) 180

2 : 12/8/44

- The nutritional status of Cambridge school-children. (J. Yudkin) 201-205
Nutrition and scholastic attainment. (I. F. MacKenzie) 205-207
Koilonychia and its recovery in cases of thyrotoxicosis. (L. Cooke & S. M. Lury) 207-209
Histological effect of injection of mepacrine (stebrin) dihydrochloride. (F. Hawking) 209-210
Sterilization of the skin by colourless flavine (5-amino-acridine). (V. Bonney & H. S. Allen) 210-211
Pituitary cachexia treated with corticotrophic hormone. (R. E. Hemphill & M. Reiss) 211-213
Trachoma in London: the end of a chapter. (A. Sorsby) 220-221

2 : 19/8/44

- Scurvy: a survey of fifty-three cases. (R. B. McMillan & J. C. Inglis) 233-236
Urinary reactions and desensitization in allergic recipients after serum transfusions. (K. Maunsell) 236-239
Incidence of bleeding gums among R.A.F. personnel and the value of ascorbic acid in treatment. (W. P. Stamm, T. F. Macrae & S. Yudkin) 239-241
Incidence of gingivitis in the Royal Air Force. (G. A. Smart) 242-244
Rupture of aortic aneurysm into the duodenum. (J. E. Morison) 244-245

2 : 26/8/44

- Psychological medicine and the family doctor. (R. D. Gillespie) 263-268
An episode of "homologous serum jaundice." (W. H. Bradley, J. F. Loutit & K. Maunsell) 268-269
Late results of closed intrapleural pneumolysis. (P. W. Edwards, A. C. Penman & J. Logan) 270-272
High-tone deafness in school-children simulating mental defect. (M. D. Sheridan) 272-274
An "explosive" outbreak of haemolytic streptococcal tonsillitis on an R.A.F. station. (T. S. Wilson) 275-276
Treatment of rheumatoid arthritis with bismuth. (A. H. Douthwaite) 276
"Having your likeness taken": observation in the student's training. (F. Roberts) 284-286

2 : 2/9/44

- Some general considerations on higher or postgraduate medical studies. (F. M. R. Walshe) 297-300
Use and abuse of trichlorethylene. (G. E. H. Enderby) 300-302
Treatment by movement. (J. Cyriax) 303-305
Fatal case of mustard gas poisoning. (F. B. Hobbs) 306-307
Heparin in intravenous infusions, including penicillin therapy. (P. Martin) 308

Bulletin of War Medicine

4 : July 1944

- A review of recent Russian studies of gunshot wounds of the thigh. (I. Aird) 619-620

Edinburgh Medical Journal

51 : May 1944

- The controversy on contagiousness *versus* non-contagiousness of leprosy: with particular reference to Dr. W. Munro's contributions published in the *Edinburgh Medical Journal*. (E. D. W. Greig) 209-214
Some problems of communal feeding. (C. P. Stewart) 213-228
Abdominal pain in pregnancy. (E. C. Fahmy) 229-246
Biochemical classification of coliform bacilli in sputum. (R. Salm) 247-251

51 : June 1944

- War wounds of the abdomen. Report of sixty-four cases treated by laparotomy. (A. G. R. Lowdon) 257-279
Propylene glycol vapour as an air disinfectant—I. (S. W. Challinor & J. P. Duguid) 280-289
Experimental cancer research. (J. F. Riley) 290-299

Journal of Endocrinology

4 : July 1944

- The artificial induction of lactation in the bovine by the subcutaneous implantation of synthetic oestrogen tablets. (S. J. Folley & F. H. Malpress) 1-18
Fracture of the pelvic bones in bovines implanted with tablets of synthetic oestrogens. (A. T. Cowie) 19-22
Artificial induction of lactation in bovines by oral administration of synthetic oestrogens. (S. J. Folley & F. H. Malpress) 23-36
The chemical composition of bovine mammary secretions induced by the subcutaneous implantation or oral administration of synthetic oestrogens. (S. J. Folley & F. H. Malpress) 37-42
Experiments on the use of tablets containing 50 % hexoestrol for the artificial induction of lactation in the bovine. (S. J. Folley, D. L. Stewart & F. G. Young) 43-52
Oestrogen treatment of cattle: induced lactation and other effects. (J. Hammond & F. T. Day) 53-82
Oestrogen excretion in milk from oestrogenized cattle. (W. Lawson, S. W. Stroud & P. C. Williams) 83-89
Induction of lactation in heifers by a single injection of esters of diethylstilbestrol. (A. S. Parkes & R. E. Glover) 90-102

Journal of Laryngology and Otology

59 : January 1944

- Injury to the ears among battle casualties of the Western Desert. (E. G. Collins) 1-15
A comparative report on ear, nose and throat work in the Army at home and overseas. (J. R. Birrell) 16-31
Sarcoma of the middle ear and mastoid. (A. C. Maconie) 32-35
Skin grafting in frontal sinus operations. (W. H. Bradbeer) 36-37

Journal of Tropical Medicine and Hygiene

47 : February-March 1944

- The cultivation of the lepra bacillus. (C. L. Trout) 1-2

47 : April-May 1944

- Eye changes in trypanosomiasis. (J. G. Scott) 15-17
Alleged medicinal and dietetic properties of the algarrabo. (K. V. Earle) 17-18
Vincent's gingivitis treated with sulphathiazole. (K. V. Earle) 18-19
Prophylactic treatment of bilharzia infection. (F. G. Cawston) 20

47 : June-July 1944

- Filariasis in the white man. (H. Neumann) 25-28
Investigations into the aetiology of exanthematic typhus. (G. Spact) 28-30

Lancet

2 : 29/7/44

- Rehabilitation of the injured in this war and the last. (H. A. T. Fairbank) 131-134
Naval experience in relation to a National Health Service. (S. Dudley) 134-137
Burns in warfare. (N. J. Logie) 138-140
Treatment of varicose veins by diathermy. (R. A. Smith) 141-142
Synergic action of penicillin and sulphonamides. (J. W. Bigger) 142-145
Traumatic retroperitoneal rupture of the duodenum. (P. A. Trafford) 145-146
Relapse of quartan fever after 12 and 21 years. (P. G. Shute) 146
Growth at home and at school. (E. M. Widdowson & R. A. McCance) 152-153

2 : 5/8/44

- Primary tuberculous infection in nurses: manifestations and prognosis. (M. Daniels) 165-170
Resuscitation of battle casualties. (D. S. Dick) 170-172
Intra-oral splint for facial palsy. (A. G. Allen & D. W. C. Northfield) 172-173
Note on a commonly unrecognized type of injury to the cervical spine and spinal cord in association with head injuries. (F. M. R. Walshe) 173-175
Antibacterial values of ethylene glycol monophenyl ether (phenoxetol). (H. Berry) 175-176
Phenoxetol in the treatment of pyocyanea infections. (J. Gough, H. Berry & B. M. Still) 176-178
Spontaneous rupture of the oesophagus. (J. L. Collis, D. R. Humphreys & W. H. Bond) 179
A note on the Thomas splint. (C. A. Pannett) 180

2 : 12/8/44

Major complications of penetrating wounds of the chest. (A. L. d'Abreu, J. W. Litchfield & C. J. Hodson) 197-201
Primary tuberculous infection in nurses: manifestations and prognosis. (M. Daniels) 201-204
Processing of plasma with kaolin. (M. Maizels) 205-208
Crush kidney syndrome in the cat. (M. G. Eggleton) 208-210
Treatment of typhus with anti-typhus horse serum. (M. Wolman) 210-212
Psychiatric casualties from the Normandy beachhead: first thoughts on 100 cases. (C. Anderson, M. Jeffrey & M. N. Pai) 218-221

2 : 19/8/44

A year of military medicine in India. (A. W. D. Leishman & A. R. Kelsall) 231-235
Wounds of the joints. (H. Fruchaud) 235-238
Acridines in septic wounds: use of 5-amino-acridine. (H. R. G. Poate) 238-240
The talocalcaneal articulation. (F. W. Jones) 241-242
Air-embolism in criminal abortion. (D. Teare) 242
Estimation of thiouracil in urine. (A. B. Anderson) 242-243
The orthopaedic anaesthetist. (B. G. B. Lucas & I. A. G. L. Dick) 243-244
Primary tuberculous infection in nurses: manifestations and prognosis. (M. Daniels) 244-246

2 : 26/8/44

Intrathoracic metallic foreign bodies. (A. L. d'Abreu, J. W. Litchfield & C. J. Hodson) 265-268
Clinical trial of globin insulin and other insulins with delayed action. (J. C. Eaton) 269-270
Aneurysm of the anterior tibial artery: with a note on arteriography. (M. Fallon) 270-272
Treatment of perforating corneal ulcer. (E. M. G. Galton) 272-273
Tetra ethyl thiuram monosulphide in the treatment of scabies. (D. B. Bradshaw) 273-275
Bronchial asthma treated by breathing exercises. (H. I. Weiser) 274-276

2 : 2/9/44

Hepatitis after yellow fever inoculation: Relation to infective hepatitis. (G. M. Findlay, N. H. Martin & J. B. Mitchell) 301-307
Cardiac neurosis as a manifestation of hypoglycaemia. (R. Greene) 307-308
Eosinophilia with pulmonary disease on return from the tropics. (J. Apley & G. H. Grant) 308-309
Note on scalp closure. (H. Gillies) 310-311
Outbreak of pneumonia in smallpox contacts. (H. T. Howat & W. M. Arnott) 312
Superior sulcus tumour (Pancoast). (B. A. Dormer, F. J. Wiles & J. Friedlander) 312-313

Public Health

57 : May 1944

Some aspects of cardiovascular disease with special reference to public health. (G. E. Donovan) 85-88
Tuberculosis and housing. (H. J. Peters) 89-92

57 : June 1944

Legislative measures against the spread of venereal diseases in Sweden. (R. J. M. Hallgren) 96-99

57 : July 1944

The nutritional status of factory workers. (J. Yudkin) 109-111
Minimum requirements in the examination of tuberculosis home contacts. (B. C. Thompson) 111-113

Proceedings of the Royal Society, B

132 : July 1944

Morphine-like properties of diphenylethylamine and related compounds. (E. C. Dodds, W. Lawson & P. C. Williams) 119-132
The shape of the human being as a function of time. (P. B. Medawar) 133-141
Studies on the absorption of subcutaneously implanted tablets of hexoestrol. (S. J. Folley) 142-163
The response of the bovine ovary to pregnant mares' serum and horse pituitary extract. (S. J. Folley & F. H. Malpress) 164-188
Ovarian stimulation by oestrogens: effects in immature hypophysectomized rats. (P. C. Williams) 189-199

Transactions of the Royal Society of Tropical Medicine and Hygiene

37 : February 1944

A survey of tropical diseases as seen in the Middle East. (E. Bulmer) 225-242
Bacteriophage therapy in bacillary dysentery. (J. S. K. Boyd & B. Portney) 243-262
Serological examination and a cutaneous test in the diagnosis of bacillary dysentery. (F. Dreyfuss & J. Gurevitch) 263-270
Pentamidine in the prevention and treatment of trypanosomiasis. (L. Van Hoof, C. Henard & E. Peel) 271-280
The sickling phenomenon in the blood of West African natives. (R. W. Evans) 281-286

37 : March 1944

Important diseases affecting West African native troops. (R. M. Murray-Lyon) 287-302
Pigment metabolism and renal failure in acute sulphonamide haemolysis resembling blackwater fever. (H. Foy, J. Gluckman & A. Kondi) 303-319
Technique and interpretation of the Weil-Felix test in typhus fever. (A. Felix) 321-341
Note on the preparation of suspensions for the Weil-Felix test. (R. F. Bridges) 343-344

37 : May 1944

Heat effects in British service personnel in Iraq. (T. C. Morton) 347-372
Lizard filariasis: an experimental study. (T. B. Menon, B. Ramamurti & D. S. Rao) 373-386
Portal cirrhosis in Iraq. (R. S. Stacey) 387-398
Lobar pneumonia in African soldiers. (T. Simpson) 399-407
Kala-azar in East Africa. (A. C. E. Cole) 409-435
Cutaneous leishmaniasis in Nigeria. (B. G. T. Elmes & R. N. Hall) 437-439
Abdominal pain in the diagnosis of early kala-azar. (E. Burke) 441-445
An unusual case of kala-azar successfully treated with stilbamidine. (M. A. Shellim) 447-449
Asthma produced by *Ascaris* infestation. (K. V. Earle) 451-452

British Medical Bulletin is published by the British Council. One volume will appear each year, and each volume will contain a maximum of 12 parts, issued at approximately monthly intervals. The object of the Bulletin is to provide a guide to medical work in Britain. Requests from overseas for further information on any of the investigations reported, or for general information, bibliographies, and particulars of medical books and journals published in Britain should be addressed to the British Council, Medical Department, 3 Hanover Street, London, W.1, England

BRITISH MEDICAL BULLETIN

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NUTRITION

SPECIAL CONTRIBUTIONS

NUTRITIONAL SCIENCE IN MEDICINE	
by Sir Edward Mellanby	202
ASPECTS OF NUTRITIONAL RESEARCH	
by Dr. B. S. Platt	204
PROTEIN METABOLISM	
by Dr. D. P. Cuthbertson	207
AN EVALUATION OF THE VITAMIN-C POSITION	
by Dr. S. S. Zilva	217
OBSERVATIONS ON WATER METABOLISM	
by Dr. R. A. McCance & Dr. W. F. Young	219
MINERALS IN HUMAN NUTRITION	
by Dr. E. M. Widdowson	221
NUTRITIONAL FACTORS IN DENTAL CARIES AND PARODONTAL DISEASE	
by Dr. J. D. King	222
DETERMINATION OF VITAMINS : PHYSICAL, CHEMICAL, MICROBIOLOGICAL	
by Dr. J. R. P. O'Brien	225
SOME PRINCIPLES OF WAR-TIME FOOD POLICY	
by Dr. M. Pyke	228

REVIEW OF SELECTED PAPERS

Assay of Vitamins in Foods and Body-Fluids

Comparative Tests of Vitamin B ₁ Content of Flour	231
Azo Colour Reaction for Vitamin B ₁ in Flour	232
Nicotinic Acid and Riboflavin in Beef Extracts and Corned Beef	232
Riboflavin Content of Mixed Diet	233
Statistical Examination of Vitamin-A Assays	233
Apparent Vitamin C in Foods	233
Estimation of " True Ascorbic Acid " in Urine	234
Estimation of " True Ascorbic Acid " in Blood	234

Studies on Vitamin C

Complement Activity and Vitamin C	234
Vitamin-C Level in Pregnancy	235
Assessment of Vitamin-C Nutrition	235
Vitamin-C Nutrition in a Hospital	235
Scurvy : a Survey of 53 Cases	236

Water Metabolism

Effects of Drinking Sea-Water	236
Study of Dehydration	237
Urine Secretion during Dehydration and Rehydration	237
Water Metabolism in Infants	238
Renal Function of Newborn Infants	238

Mineral Metabolism

Changes in Calcium Metabolism in Man	238
Effect of Bread on Absorption of Calcium	239
Relative Antirachitic Value of Carbonate and Phosphate of Calcium	239
Increasing Calcium Absorption by Administration of Protein Derivatives	239
Phytic Acid and Iron Absorption	240

Vitamin-B Complex : Nitrogen

Studies in Vitamin-B Deficiency	240
Problems in Riboflavin and Allied Deficiencies	240
Potato as a Source of Dietary Nitrogen	241
Value of Dietary Mixed Proteins	241

Vitamins and Bone-Growth

Effect of Vitamin-B Complex on Fibroblasts	242
Experiments on Vitamin C and Calcification of Bone	242

Ocular Manifestations of Nutritional Deficiency

Ocular Signs of Riboflavin Deficiency	243
Corneal Vascularization in Nutritional Deficiency	243
Amblyopia due to a Vitamin Deficiency	243

[continued overleaf

REVIEW OF SELECTED PAPERS—continued

Disease of Teeth and Buccal Cavity	
Mottled Enamel, M-Hypoplasia and Dental Caries	243
Improved Dentition of London School-Children	245
Fluorine and Dental Caries	246
Bleeding Gums and Gingivitis in the Navy	247
Gingival Disease in Children	247
Incidence of Gingivitis in the Royal Air Force	249
Incidence of Bleeding Gums in the Royal Air Force and Treatment with Ascorbic Acid	249
Stomatitis due to Riboflavin Deficiency	249

Nutrition and Physical Fitness	
Effect in School-Children of Vitamin Supplements	251
Deficiencies of Vitamins A and C in School-Children	251
Effects in Girls of Vitamin and Mineral Supplements	251
Effects in School-Children and Factory Workers of Vitamin Supplements	252
Growth of Children at Home and at School	252
Nutritional Status of Cambridge School-Children	252
Nutritional Status of School-Children from Industrial Towns	253
Nutrition and Scholastic Attainment	253
Nutrition and Size of Family	253
Effect of Nicotinamide on Muscular Effort	253

Diet and Disease : Communal Feeding	
Nutrition in the Pathogenesis of Disease	253
Effects on Rats of an African Diet	254
Problems of Communal Feeding	254
Value of the Midday School Meal	254

BOOKS, MEMORANDA, REPORTS	255
GUIDE TO THE JOURNALS	256

For two reasons, we are particularly glad to be able to publish a contribution from SIR EDWARD MELLANBY. The first, and more obvious, reason is that this number is concerned with nutritional problems, and Mellanby is well known, not only as the official leader of British medical research, but as one of the builders of nutritional science. An essay on nutritional science in medicine from such a source cannot fail to command special interest and attention. The second reason is that Sir Edward Mellanby has been, since 1941, Chairman of the Medical Panel which advises the British Council in that part of its work which is directed to the development of medical relations with other countries. Any progress which this work has made has been to a large extent dependent on Sir Edward's advice, encouragement and accessibility.

Most readers will know that it was Mellanby who proved rickets to be a disease primarily due to the absence from the diet of a fat-soluble factor (later to be identified as vitamin D). It is perhaps less well known that he was also the first to show (in 1922) that cereals exerted a rachitogenic influence. In 1939, he (with D. C. Harrison) identified phytic acid as one of the factors responsible for this influence. Phytic acid exercises its rachitogenic action by precipitation of dietary calcium as the insoluble calcium phytate. It was an idea of considerable novelty that something in the nature of a simple test-tube reaction, taking place in the alimentary canal on admixture of the reagents concerned, could affect the availability of an important nutrient. This work was extended by investigations on the effect of brown bread on mineral metabolism (see notes on Dr. McCance and Dr. Widdowson below), and has led to the fortification with calcium of the British war-time loaf. Mellanby has recently (*Nature*, 1944, 154, 394) drawn attention to the complex factors which may affect the amount of phytic acid and its hydrolytic products present in cereal foods in the form in which they are consumed.

Mellanby has also in recent years been responsible for another piece of research which may well throw light on a number of unsolved clinical problems. This was the discovery that vitamin A influences the growth and shape of bones and, indirectly, the function of the central nervous system and its nerves (including those pertaining to the special senses) as they traverse bony canals. We have already published brief

references to this work (*BMB* 97 & 376), which was recently summarised in Mellanby's Croonian Lecture to the Royal Society (*Proc. roy. Soc. B*, 1944, 132, 28).

Mellanby's earlier scientific activity has included an investigation into the effects of alcohol on the human organism, made in 1918 at the request of the British Government, and also work in the fields of cancer and endocrinology. From 1930 he was actively associated with the Health Section of the League of Nations and was Chairman of the International Conference for Standardization of Vitamins in 1931 and 1934 and of the International Technical Commission on Nutrition. Among nutritionists he is regarded as the driving force behind the establishment of international standards of vitamins and of standards for optimal human nutrition.

In 1933 he became Secretary of the Medical Research Council, the second to hold that office, and under his administration the Council has initiated or supported an extraordinarily wide field of medical research activities. Since 1939, more long-range activities have had to yield precedence to medical problems of the war, and a full account of these will make interesting and impressive reading when it can be published. In particular, the work of the committees, under Mellanby's chairmanship, which have been responsible for the study of numerous physiological and psychological problems of the fighting personnel of the Navy, Army and Royal Air Force, will deserve attention. For an authoritative and thoughtful discussion of problems of the organization and direction of medical research in normal times, the reader should refer to Mellanby's Harveian Oration on 'The State and Medical Research' (1937).

DR. B. S. PLATT, the author of our second article, is Director of the Human Nutrition Research Unit recently appointed by the Medical Research Council. Dr. Platt started as a chemist and then turned to the study of medicine. He has had a unique experience of nutritional investigation in the field. From 1932-38 he was with the Henry Lester Institute of Medical Research at Shanghai, and while there carried out original investigations on vitamin deficiencies, for which he had a dual qualification as physician and chemist. In 1938 he returned to Britain and was appointed to the scientific staff of the Medical

Research Council as senior member of the Central Organization for Co-ordination of Nutritional Investigations in Colonial Territories. From 1938-40 he was director of a survey in Nyasaland, in the course of which he visited (for the Secretary of State for the Colonies) Uganda, Kenya, Tanganyika, Zanzibar, North and South Rhodesia, and Bechuanaland. In 1940 he became Joint Secretary of the Scientific Committee on Food Policy, which advises the British Government. Between 1940 and 1942 he was responsible for surveys of feeding in industry, in the Royal Air Force, and in the Army, was appointed Secretary of the Medical Research Council committee on the care of shipwrecked personnel, and became a member of several other committees concerned with medical and nutritional problems arising out of the war. In 1943 Platt represented the British Ministry of Health at the United Nations Conference on Food and Agriculture at Hot Springs, U.S.A. In the autumn of 1944 he flew to Newfoundland as one of a survey group, and he has recently left England for a visit to the British West Indies to investigate nutritional conditions (his departure on this mission has made it impossible for him to correct the proofs of his article).

DR. D. P. CUTHBERTSON was in 1943 seconded to the headquarters staff of the Medical Research Council. He is Secretary to the Council's committees on traumatic shock, blood-transfusion research, haemoglobin surveys, and protein requirements. From 1926-34 he was lecturer in pathological biochemistry at the University of Glasgow, and clinical biochemist to the Glasgow Royal Infirmary. In 1934 he was appointed Grieve Lecturer in physiological chemistry at Glasgow University.

During the past 14 years his research work has been directed mainly to the study of metabolic responses to injury, factors influencing wound-healing and the strength of bone, and the interrelationships of protein and carbohydrate metabolism. In his article he briefly surveys the difficult and far-reaching subject of protein metabolism.

DR. S. S. ZILVA, who is a member of the scientific staff of the Medical Research Council working at the Lister Institute, is well known as one of the original workers on vitamin C. He first came to the Lister Institute in 1913 and became a member of the staff of the Medical Research Council six years later. From 1927-31 he was partly seconded to the British Empire Marketing Board for the investigation of nutritional problems in connection with food products from the Empire. He has been a member of the Accessory Food Factors Committee of the Medical Research Council since 1930 and is also a member of others of the Council's sub-committees. For many years he has been engaged in the full-time study of nutritional problems, with special reference to the subject of vitamin C in its chemical, biological, physiological and pathological implications.

DR. R. A. McCANCE is Reader in Medicine at the University of Cambridge. Originally a research student in physiology, he decided to study medicine at King's College Hospital, London, with which he was associated after graduation. Work with Dr. R. D. Lawrence, the well-known specialist in diabetes, first aroused his interest in the chemical composition of foods. Later, as a result of investigations which lasted 14 years, he published (with E. M. Widdowson) a monograph on the chemical composition of foods, which was issued as No. 235 of the Medical Research Council Special Report Series. McCance's interest in water metabolism was also originally stimulated by work done with Dr. R. D. Lawrence on the secretion of urine in diabetic coma. In 1936 McCance delivered the Goulstonian Lectures at the Royal College of Physicians, taking as his subject his own work upon experimental salt-deficiency in man. The work on salt was followed by a series of investigations on the absorption and excretion of iron, calcium and other minerals (see also note on Dr. Widdowson below). In 1938 McCance was appointed to his present position at Cambridge, but this has involved little interruption of his investigations. Since the war he has devoted particular attention to balance experiments, many of which are performed upon himself and his collaborators, and involve exact measurement of all ingested food and excreta. In 1943 McCance went to Spain and

Portugal on behalf of the British Council to lecture and visit medical centres.

DR. WINIFRED F. YOUNG, who is co-author with Dr. McCance of the article on water metabolism in this Bulletin, studied medicine at Cambridge and was, in 1935, appointed as intern and resident biochemist to the diabetic clinic at King's College Hospital. Since then she has held resident appointments at the South London Hospital for Women and Children, the Infants' Hospital, Vincent Square, London, and the Children's Hospital, Birmingham. She has been the holder of a grant from the Medical Research Council from 1938 to 1943, first (1938-41) for an investigation at Birmingham on the renal function of infants and of dehydration in infants with diarrhoea and vomiting, then (1941-43) for work with Dr. McCance on the study of experimental dehydration in human volunteers at the Department of Medicine, Cambridge.

DR. E. M. WIDDOWSON, who contributes an article on mineral metabolism, started her scientific career as research assistant to the Food Investigation Board of the Department of Scientific and Industrial Research (a State-supported organization parallel in function to the Medical Research Council). From 1933 to 1938 she worked in the Biochemical Department of King's College Hospital and then moved to the Department of Medicine, Cambridge, where she is working as a whole-time member of the Medical Research Council staff. Most of her work has been on the composition of foods and on mineral metabolism in man. In collaboration with McCance, she discovered that iron is never excreted in more than traces, and consequently that the amount absorbed must vary with the needs of the body. The work on mineral metabolism led to the demonstration that brown bread inhibited the absorption of calcium, and provided experimental evidence for the addition of calcium to the war-time flour (which has a relatively high phytic-acid content). Dr. Widdowson also introduced the "individual method" of making dietary surveys, in which each person weighs all that he or she eats for a period of one week.

DR. J. D. KING was engaged in full-time research on behalf of the Medical Research Council from 1932-1940. From 1940-41 he held a commission in the Army Dental Corps and conducted an investigation on ulcerative gingivitis. In 1941 he was seconded to the Medical Research Council for further research on parodontal disease, and he has recently been appointed to the Council's whole-time scientific staff at the Nutrition Building of the National Institute for Medical Research. He is the author of a considerable number of original publications on dental and parodontal disease, with special reference to nutritional factors. These publications include one of the Medical Research Council Special Report Series (No. 241) on "Dental Disease in the Island of Lewis".

Dr. King has co-operated with the Ministry of Health in war-time surveys related to nutrition and oral health.

DR. J. R. P. O'BRIEN is at present demonstrator and lecturer in clinical biochemistry in Oxford University, and biochemist to the Nuffield Scheme for Medical Research. He was a pupil of Professor R. A. Peters, of Oxford, with whom he worked on the isolation and physiological properties of vitamin B₁ and other constituents of the vitamin-B complex. His interests are at present divided between nutritional problems associated with the B-vitamins, and the metabolism of the porphyrin pigments in blood disorders.

DR. MAGNUS PYKE started his scientific career at McGill University, Montreal, and in 1933 he took a degree in agricultural chemistry. He later carried out research in biochemistry under the direction of Professor, now Sir Jack, Drummond, at University College, London, where he received the degree of Ph.D. of that University and subsequently became a Fellow of the Royal Institute of Chemistry. As assistant to Sir Jack Drummond in the Ministry of Food, he has been concerned particularly with nutritional problems in connection with large-scale feeding. He also acquired experience, both in Canada and in Britain, in applied biochemistry, in the course of work for industrial firms engaged in the manufacture of pharmaceutical and biochemical products.

SPECIAL CONTRIBUTIONS

484

NUTRITIONAL SCIENCE IN MEDICINE

Sir EDWARD MELLANBY, K.C.B., F.R.S., M.D., F.R.C.P.

Secretary, Medical Research Council

Nutritional research has now come to occupy a dominant position in the study of problems both of health and of biological science. In regard to disease, it began as a small flame in 1897, when Eijkman correlated his observations on beriberi among Javanese prisoners with his experimental results on polyneuritis gallinarum, finding that these conditions in man and bird were both due to the consumption of polished rice, and preventable by addition of the pericarp of the grain. The flame was fanned by Holst and Frölich in 1907, when they studied scurvy in guinea-pigs and found that it could be prevented and cured by something in fresh vegetables and fruits. As both beriberi and scurvy were rarely seen in western countries, the average medical man was not particularly interested in these clinical discoveries. It was only in 1918, when it was shown by experiments on puppies that rickets, one of the most common diseases of Europe, was due to the absence from the diet of a fat-soluble substance associated with fish and animal fats, that the importance of diet in relation to human health and disease was appreciated.

Recognition of Dietary Deficiency as a Cause of Disease

From 1920 onwards, the flame of dietetic and nutritional research became a fire extending over all countries of the world. In particular, the idea of "deficiency diseases"—that is, diseases due to the absence from the body of specific chemical substances—was generally accepted. It was recognized that, for the maintenance of health, certain vitamins and other accessory factors must be present in the food in sufficient quantities, as the animal body was either incapable of synthesizing them, or its power in this respect was limited.

It is now known that this idea of "deficiency diseases" is not always so simple as when Grijns first formulated it in 1901, and that there are other dietetic and nutritional factors which often determine the development of such illnesses. Thus, the amount of aneurin necessary to prevent beriberi and allied conditions is governed by the amount of carbohydrate or alcohol also consumed; similarly the amount of vitamin D necessary to produce perfect calcification of bones and teeth is conditioned by the amount of calcium and phosphorus in the food and their relationship to one another. In other words, there are sometimes positive as well as negative factors to be taken into account in such diseases.

It would be unfair, in recording the successes that have followed the establishment of "deficiency disease" as a factor in animal and human life, to forget that the idea of such an ætiology had been advanced so long ago as 1850 by Chatin, following extensive estimations of iodine in foodstuffs, when he related the development of simple goitre to a deficient intake of iodine. This hypothesis was, however, formally suppressed by the French *Académie des Sciences* in 1860. The recognition, as a result of the discoveries of Pasteur, Lister and Koch, that a major cause of disease was the invasion of the body by micro-organisms, was responsible for an outlook which made it difficult, and at the time apparently impossible, to imagine a deficiency or absence of something from the body as being a cause of disease. It was only the discovery by Baumann in 1895 of iodine in the thyroid gland that allowed the resuscitation of Chatin's original hypothesis of the cause of thyroid enlargement, and research from that time has more and more confirmed his views.

If this disregard of dietary deficiency as a factor in disease were the only suppressive effect that could be ascribed to Pasteur's remarkable work, it would probably not be sufficiently important to stress here, but it must also be remembered that it had a similar influence on the attitude to Claude Bernard's hypothesis that many diseases are due to the abnormal working of bodily processes which, when physiological or optimal, result in good health. It will be remembered that Claude Bernard claimed, on this basis, that medical science was essentially experimental physiology. This again

was an overstatement of the case, but the success of the *materies morbi* hypothesis, as achieved by Pasteur, Lister and Koch, again delayed, but did not prevent, the ultimate acceptance of Bernard's hypothesis. Indeed the development of research on "deficiency diseases" has tended only to emphasize the truth of the Bernard teaching.

Dangers of a Specialized Outlook

There is surely a lesson to be learnt from these historical facts—namely, that we must avoid allowing the very success of research on the relation of nutrition and disease to cloak and possibly even to suppress, temporarily at least, other pathological hypotheses and theories. The specialist is the backbone of medical, as of all research, but the concentration that leads to discovery is apt to be associated with blindness to other views, and this must be guarded against. Probably the danger is not so great nowadays, when many more men and women are engaged in medical research and when publication of results is so easy and widespread, but it would be well if the danger were more widely recognized. What is more likely to happen now is, not the suppression of new points of view and new lines of scientific investigation, but the too rapid development, and adoption as a fetish by an advertisement-goaded public, of new discoveries in medicine. This undesirable reaction as regards vitamins has not been absent from some countries, and scientific men ought to combat it. Except in infancy and childhood, there are but few instances where good health cannot be maintained by eating properly chosen food without the constant administration of vitamin preparations.

Biological Problems

Surveying now the general field of nutritional science, what do we find? We see that physiologists and biochemists, mainly by means of experiments on the growth of young rats, have detected a large and increasing number of chemical substances which must be present in the diet, often in minute quantities, either for the maintenance of life itself, or for proper growth. The chemical constitution of most of these vitamins is known. The chemists' success has indeed been great. But what about the biological side: can it be said why these substances are essential and/or in what way they work? From this angle the success has not been so outstanding: a biological problem is usually much more difficult than a chemical problem, for the living cell and animal body are not limited in their actions by the known rules and regulations of the chemist's laboratory. Besides, the physiological technique which led to the discovery of many of these substances, namely growth in young animals, is so crude, and the factors involved are so many and complicated, that little knowledge of biological function can be deduced from them.

Thus, there is hardly any knowledge of how the vitamins work in performing their functions. Even when the ultimate action of a vitamin is known, as in the case of vitamin D, whose main function is certainly so to control calcium-phosphorus metabolism as to bring about the calcification of bones and teeth, there is still no knowledge of how it works. Does it simply bring about the absorption from the intestine of sufficient calcium and phosphorus to maintain these elements at an optimum level in the blood, leaving the calcifiable tissues to select their needs from the blood stream, or does it actually assist the calcification process in the bones and teeth? Even when there is sure evidence that vitamin D acts in either or both these ways, there will still remain the problem of how it performs these functions. Does it, for instance, form part of an enzymic complex analogous to the co-carboxylase in which vitamin B₁ is known to participate? In the case of vitamin D we have at least reached the stage of formulating the problem, and the same applies to vitamin K, but with most other vitamins we have not even reached this stage. Clearly this is a great

challenge to all interested in experimental biology—physiologists, biochemists, pathologists, pharmacologists and clinicians. To pathologists the appeal is specially strong, even to those concerned with morbid anatomy, for one outstanding result of modern work on nutrition is that it is gradually making that subject into an experimental science. Few things are more interesting than to see how, one by one, it is becoming possible to reproduce under experimental dietary conditions the long-known classical changes seen in morbid tissues, one of the most interesting in recent times being the fatty infiltration, necrosis and cirrhosis of the liver induced by dietary defects of choline and the amino-acid methionine.

Nutrition and Infection

Nothing seems to be more certain than that nutritional defect is at least part of the ætiological basis of many of the more common illnesses, and yet, in most of these cases, this is only conviction without satisfactory proof. For instance, it will probably be found that a dietetic or nutritional factor is involved in the ætiology of enlarged tonsils and adenoids, peptic ulcer, diabetes mellitus, pernicious anæmia, arteriosclerosis and rheumatic disease. The relation of nutrition to infection remains an unsolved problem, but that there is such a relationship is not to be doubted. Tuberculosis and other infective diseases increase when the nutritional condition of a population is greatly lowered. What is even more certain is that in badly-fed populations infective invasions by micro-organisms are much more deadly than in the well-fed.

In the great field of investigations which lies before us, we must keep a balanced view of the relative importance of the two factors—infection and resistance to infection—as influenced by nutrition. The bacteriologist and epidemiologist may, at times, be inclined to lay all stress on the infective process and the pathogenicity of the micro-organisms; the nutritionist, on the resistance of the body. The relative importance of these factors will no doubt vary greatly in each particular infective process studied, but that both must be regarded as of major importance in many cases is undoubted. We have recently seen how fruitful has been the study of some chemotherapeutic agents, especially the sulphonamides, when considered from the point of view of the chemistry of the bacteria upon which they act, and it is not to be doubted that knowledge of the chemical processes which underlie the toxic action of pathogenic micro-organisms and the resistance of the tissues to them, and of how these are affected by nutrition, will shed great light on infective disease. In some cases it may even be found that passage of an infective agent through a series of people in good nutritional state will lower the pathogenicity of the invading micro-organisms.

In some types of infection it will probably be found that diet, acting during the period of development of the affected tissues and after their formation, is the main controlling factor as, for instance, in dental caries, gingivitis and parodontal disease. In other cases good nutritional conditions may only modify the severity of the disease by increasing the resistance of the body to the infective agent, as for instance in tuberculosis, while in some types of infection the diet and nutritional state may have little or no effect on the incidence and severity of the condition.

To what extent, if any, dietary factors will be found to have a specific anti-infective action remains for future investigation. Some investigators on nutrition have already had experience in the search for this El Dorado, and in consequence regard the problem with more respect. Nothing could have been more promising than the indications of a specific anti-infective action of vitamin A in young rats, which die almost without exception with multiple infective foci when deprived of vitamin A, and recover rapidly if this vitamin or carotene is added to the diet within reasonable time. In endeavouring to extend these facts to bacterial infection in human beings two points were not realized. The first, that rats hold a special place among animals in their susceptibility to infection when deprived of vitamin A, because of their great liability to develop hyperplasia and metaplasia of epithelial surfaces under this condition. The second, that it seldom happens that human beings are deprived of vitamin A to the extent produced experimentally in the rat experiments. Although it is undoubtedly true that a great deficiency of vitamin A in the body lowers man's resistance to bacterial infection, it is improbable that a degree of deficiency of this vitamin, such as is met with in Britain

and comparable countries, is an ætiological factor in infective disease of great significance, except possibly in infants. Nor is there any substantial evidence in the case of vitamin A that added resistance to infection results from giving more of it than is physiologically needed. Indeed there is but little evidence that giving amounts of any vitamin larger than those physiologically necessary makes the body functionally more effective. An exception to this is nicotinamide which, in larger doses than are necessary for health, appears to produce an effect on the neuro-muscular mechanism in man which lowers the time needed to carry out strenuous exercises associated with good co-ordination.

Nutritional Science and Food Policy

War conditions in Britain have made it essential for the maintenance of health that modern knowledge of nutrition as revealed by research should play an important part in framing food policy. War-time food policy in this country, as carried out by the Ministry of Food, is described in a separate article below.* It might be of interest to say something from the point of view of the scientist on this question. It can be said at once that during war-time nutritional experts in Britain have had an opportunity to express their views and to give their advice either through the *Medical Research Council* or through the Food Policy Committee of the War Cabinet. Generally speaking, actions by the Ministry of Food have followed the lines of this advice, sometimes on the basis of its nutritional advantages to the nation, and occasionally because the shipping and economic conditions enforced its adoption. As the scientists' advice on food policy in war-time was based on both of these factors, it came to the same thing in the end, but this will not necessarily continue to be so when the time comes to adopt a long-term policy for the days of peace. When that time arrives, policies dependent on scientific and economic factors respectively will often be divergent and, unless the nutritional needs of the people are given precedence over economic claims, much of the progress in health standards of the population may be lost.

The war has emphasized the lesson that in industrialized countries two foodstuffs have pre-eminent claims to national control. The first is milk and the second cereals, especially bread. So far as milk is concerned, the policy of Britain is satisfactory and will probably remain so in peace-time. In this case the Government policy to ensure that all pregnant and nursing mothers and all infants and children receive, if they so wish, a reasonable quantity of milk can only be commended. It is true that in war-time many adolescents and adults have had to go short of milk, especially in the winter months, and it is also true that too high a proportion of the milk is neither clean nor bacteriologically safe. Determined action is required both to increase the supplies and to improve the quality, and the Government seems inclined to press on with both of these policies.

The Bread Question

In the case of cereals and cereal products, the situation is not so satisfactory. Bread made from wheat has in the past formed, and undoubtedly will in the future, a substantial part of the British diet. The bread eaten before the war was made of a low-extraction flour (70 to 73 % of the berry), and consisted entirely of the endosperm, while the bran, aleurone layer, scutellum and embryo were extracted by the millers and sold for cattle, pig, and poultry food. Thus, most of the vitamin and mineral contents of the wheat berry which are known to be essential for health went to animals, while the residue formed a substantial part of human dietary. Nutritional scientists are agreed that this policy is wrong, but unfortunately there are two schools of thought as to the best method of dealing with this important national problem. One school, represented by British scientists, thinks that bread for human consumption should be made of flour containing as much of the wheat berry as is physiologically absorbable, i.e. the whole grain except for the outer coarse bran. The second school, represented by some North-American scientists, thinks that flour should be of the old low-extraction, white type, with the addition of those vitamins prepared by synthetic or other methods which are known to be present in the original berry. This second method is based on the assumption that the main vitamin contents of cereals are known, and that their physiological importance

* [see *BMB* 492]

to the body is understood. These assumptions many physiologists will find difficult to accept. It is probable that the policy of the British Ministry of Food in war-time as regards bread production, namely of producing 85 % extraction flour with a minimum of fibre and with high vitamin-B₁ and iron content, has depended more upon shipping difficulties than upon nutritional grounds. Consequently, when the shipping situation is eased, there will be a powerful move to return to the meretricious attractions of the old white bread for human consumption, thus releasing to the farmer, poultry-keeper and manufacturer of proprietary food-products more of the valuable offal for their own purposes. Possibly as a gesture to those with knowledge of nutrition there will be added to the bread aneurin, nicotinamide, riboflavin and iron, as is now being done in North America.

This solution of the bread problem, which consists essentially of depriving flour of most of the chemical entities in wheat which are necessary to life and then restoring a few of these substances, seems wrong in principle. In fact, the method is also wrong, because the low-extraction white flour will undoubtedly be more and more eaten in tropical and other countries in which the addition of the vitamins will not take place. There will be a repetition of the polished rice story, only in this case it will be soulless bread.

Need for International Agreement

It is obvious that scientists of different countries cannot afford to differ on this important question of the best utiliza-

tion of available foodstuffs. In the case of cereals, and particularly bread, it is very desirable that after the war they should come together and see whether they cannot reach agreement on the optimum composition, both from a nutritional and from an æsthetic point of view, of those cereal preparations which form such a large proportion of the normal diet. The path to such an agreement in policy has already been blazed by the Health Section of the League of Nations. This body achieved the outstanding feat, both of setting up international standardization of vitamins, and also of determining standards of nutrition in terms of common foodstuffs. Probably after the war either this body or its successor will be able to bring about further international co-operation in matters of diet and nutrition and, among other things, agree on a common policy as regards the optimal composition of bread and other cereal products. It may be that new milling techniques will have to be introduced to secure the production in peace-time of bread which fully accords with the principles advocated by British scientists: namely, bread made from a flour which contains all the nutritionally important contents of the wheat berry and is at the same time æsthetically excellent.

All that is demanded is that the factor controlling the constitution of bread should be primarily the health of the consumer, and that milling and other interests should be secondary to this condition. Indeed, no nutritional policy adopted by governments can be wrong if it places the health and the needs of the community as its first and guiding principle.

485

ASPECTS OF NUTRITIONAL RESEARCH

B. S. PLATT, M.Sc., Ph.D., M.B., Ch.B.

Human Nutrition Research Unit, Medical Research Council

The science of nutrition has grown rapidly in recent years; there has been an almost equally rapid application of nutritional knowledge in public health and social and economic problems the world over. In this essay, I want to illustrate from my own work, and from work with which I have been intimately associated, the nature of the most important phases of the progress made in nutritional science and in its practical application.

Types and Grades of Nutritional Deficiency

The advances made in nutritional science in the present century have mainly originated in the study of dietary deficiency disease. It is now well recognized that such diseases as rickets, beriberi, scurvy and pellagra are caused by lack of specific chemical substances or nutrients in the diet. In general, these are primary dietary diseases; symptoms and physical signs similar to those found in these diseases may, however, develop secondarily to conditions in the body which give rise to impaired absorption and utilization, or abnormally increased requirements, of the specific nutrient.

The grade of a deficiency disease, whether primary or secondary, depends on the *degree* of the insufficiency of the food factor and its *duration*; the degree may be mild, moderate or severe, the duration acute, subacute or chronic.

Observations made in a combined biochemical, clinical and field investigation of many hundreds of cases of vitamin-B₁ deficiency in China from 1933 to 1937 (Henry Lester Institute, 1935, 1936a, 1937-38a; Platt & Gin, 1934; Platt & Lu, 1935, 1936) will assist, perhaps better than those on any other deficiency disease, in elucidating the various ways in which a primary dietary deficiency may manifest itself. In acute severe vitamin-B₁ deficiency the patient was obviously seriously ill, was either greatly distressed, or sometimes collapsed, and, before the highly concentrated or pure vitamin B₁ was available, invariably died. Pyruvic acid was isolated from the blood of patients with this acute, severe vitamin-B₁ deficiency. It was found that this substance accumulated in the blood up to a level of 5 to 6 mg. per 100 ml. A single dose of 5 mg. of pure vitamin B₁ was usually sufficient to reduce this to the normal level of about 0.5 mg. per 100 ml. in 12-15 hours, with complete recovery of the patient. In striking contrast to this type is the chronic so-called "dry" beriberi. There is no accumulation of pyruvic acid in the

blood of this group of patients, and treatment for long periods appeared to have little or no effect.

By far the largest group of beriberi cases encountered in Shanghai were of subacute, mild or moderate deficiency. There was usually a small accumulation of pyruvic acid in the blood; the signs and symptoms had some of the features of the acute, the severe and the chronic types, but they responded to treatment with vitamin B₁ more slowly than the former but much more markedly than the latter grade.

Observations (Henry Lester Institute, 1936b) on the effect of the treatment of scurvy with pure vitamin C, and of gross follicular keratosis with vitamin-A concentrates, though less extensive than those on beriberi, were sufficient to justify the view that these diseases could exist as primary dietary defects in substantially "pure" forms. At the time this work was done, the components of the vitamin-B₂ complex had not been separated, but pellagrins were observed to recover rapidly on treatment with certain liver concentrates now known to be rich in nicotinic acid.

Factors Contributing to the Clinical Expression of Nutritional Deficiency

Added to the effects of degree and duration on the manifestations of vitamin-B₁ deficiency, were the consequences of various stress factors. These included physical exertion, the amount of rest and sleep obtained, the quantity of carbohydrate foods in the diet, the temperature and humidity of the climate, the co-existence of infections (particularly those associated with fever) and the concurrence with the deficiency state of hyperthyroidism. Thus, the onset of the majority of beriberi cases coincided with the onset of the hot humid season of the year. Patients with the acute severe disease were usually admitted to hospital in the early hours of the morning after a sleepless night due to poor sleeping quarters and bad hygienic conditions, including infestation with bed bugs. Characteristically, patients of this group were young hard-working males, accustomed to eating large meals consisting mainly of highly milled, well washed rice.

The manifestations of deficiency observed in pregnancy are of special interest (Platt, 1937), in that they illustrate how stress factors and duration can contribute at different stages to the appearance of different signs and symptoms. Towards the end of pregnancy, when there is already strain on the

circulatory system, the signs and symptoms of nutritional deficiency are predominantly cardiovascular, such as swelling of the feet towards the end of the day, with breathlessness on exertion. This evidence usually disappears with parturition, and if dietary insufficiency persists and lactation ensues, a well-defined polyneuritis may develop.

Stress factors also play their part in determining the site of a lesion. Thus, the peripheral neuritis of vitamin-B₁ deficiency may be most marked in the most used parts of the body. A man stripping hides with a knife held in the left hand, the right hand holding the hide, showed changes in the left upper limb only; a tailor's cutter had a right "thumb drop" and a tram driver had changes most marked in the upper arms. Pressure may prove to be a localizing factor, for example, follicular keratosis due to vitamin-A deficiency may be found only on the right forearm in women who do not show such changes elsewhere; these women will be found to rest their forearm on their knee when shelling maize or peeling plantains in a squatting position. Exposure to sunlight is a factor in determining the areas of the skin affected in a pellagrin.

In addition to the combination of dietary deficiency and various stresses, zymotic disease factors may play a part in determining or modifying the clinical picture as, for example, in the association of the fusiform bacillus and spirochaetes of Vincent's disease in the gums in nicotinic-acid deficiency in sites where there is local trauma or irritation. The organism (*Oidium albicans*) associated with "thrush" may develop on an excoriated area, and an angular stomatitis thus infected becomes "la perleche".

Early Observations on the Occurrence of Minor Deficiency States

Once the ætiology of the frank cases of deficiency diseases, resulting mainly from insufficiency of single food factors, was recognized and the therapeutic measures became available, the centre of interest in malnutrition shifted to the study of minor manifestations of insufficiency of these and other accessory food factors. In a summary of a lecture I gave in 1936 (Platt, 1936a) it is stated:

"Emphasis is laid on the discovery of the prevalence of the manifestations of minor grades of dietetic deficiency diseases, in the study of which it may be taken as a general principle that the knowledge of the natural history of these various diseases and their uncomplicated and more flagrant forms, provides the basis for identification in their larval stages."

Some of these minor manifestations I described as occurring in associations, particularly with the minor manifestation of vitamin-B₁ deficiency, and in summarizing observations of their incidence I wrote (Henry Lester Institute, 1937-38b):

"In 1933-34 the occurrence of various clinical manifestations in association with beriberi was recognized. These were evidently early stages of deficiency diseases not sufficiently well developed to be called scurvy, pellagra, etc. Observations were made on numerous subjects in factories, workshops, schools and on inhabitants of rural areas using these signs as indices of improper nutrition. The results obtained showed that in industrialized areas, especially amongst the younger workers, there was a high incidence of malnutrition measured by this method. Furthermore there were very many cases of minor grades of deficiency for each frank case of deficiency disease recognized. Of nearly two thousand so-called apprentices in small workshops in Shanghai 70 % showed at least one deficiency sign. These boys comprised 40 % of the total working force. Owing mainly to the deficiency diseases which had developed, a large turnover was found; 60 % worked one year or less and in a sample of 200 workers 15 % had been replaced in three months. A high proportion of the deficiency states met with were due to vitamin-B₁ deficiency.

"The knowledge of the appearance of these forms of impaired nutrition served as a basis for a general survey of the population in some refugee camps. These results, from samples of 50-100 persons taken from each of six refugee camps containing some 1,500 refugees at the end of August 1937, showed that, in a total of 400 refugees, 117 had evidences of vitamin-B₁ deficiency, 11 of these being established beriberi. These subjects had not been in the camps for more than ten days and the evidences of deficiency must have been due to deficient diets taken before the war situation developed. It is interesting that the distribution of evidences of vitamin-B₁

deficiency in this sample of population is similar to that found by us in the previous year for young factory boys."

Effects on Nutrition of Food Habits and Methods of Preparation of Food

The study under discussion also included an investigation of the dietaries of the patients, most of whom came from small factories where they worked, ate and slept, few surviving two summers without sickening, dying or being sent back to their homes in the country. Their food seemed at first sight to be similar to their home diets in that they ate mainly rice, occasionally wheat products, vegetables, soya bean preparations and a little meat and fish. But when enquiries were extended into the villages from which the city's labour was recruited, important differences emerged. Small, occasional but precious, additions to the dietary made by the mother in the home were not included in the food provided by the city contractor who, in order to cater at the cheapest possible rate, also bought stale vegetables and inferior grades of rice. The rice had not only been highly milled in the first place but often, owing to the growth of a mould during storage, it had to be re-milled and then vigorously washed to make it fit to eat. This high degree of milling, combined with excessive washing, removed all but a small fraction of the vitamin B₁ in the grain. In the rural areas, on the other hand, the rice was usually freshly prepared from grain stored in "paddy" form, i.e. with the husk on, was home-pounded and therefore not highly milled, and did not need to be thoroughly washed. In an experiment carried through in the summer of 1937 and only just completed at the outbreak of the Sino-Japanese war (Platt, 1939), it was found that, by using rice processed by mechanical means, but following lines similar to the traditional methods, the occurrence of signs and symptoms of beriberi could be entirely prevented.

This experiment illustrated the importance of taking into account food habits and practices. Another valuable illustration is afforded in work done on infant feeding in China (Platt, 1936b; Platt & Gin, 1938). A first reaction to this problem, in the absence of cow's milk, is to find a substitute, as witness the attempts to use soya bean milk with various additions. The Chinese in their wisdom, however, point the way to the most satisfactory solution by making every effort to ensure the supply of mother's milk over a long period and, if this fails, to secure human milk by a system of wet-nursing which does not necessarily deprive the foster-mother's own infant.

Social Factors Revealed by an African Survey

In 1938 I began work as a member of the staff of the *Medical Research Council* along the lines set out in the first report of the Committee on Nutrition in the Colonial Empire. This Committee's work may be traced back to the stimulus given to co-ordination of effort in health and agriculture by the Health Organization of the League of Nations, an account of which will be found in the report of the League of Nations Mixed Committee on Nutrition (1937). Part I of the report of the Committee on Nutrition in the Colonial Empire (1939) which, for the most part, can still be recommended for study and application, brings out the many-sided nature of the problem of nutrition under a wide variety of conditions, and on the recommendation of the Research Sub-Committee a combined survey was carried out in Nyasaland in 1938-40. This comprised four sections: (i) economic and agricultural survey; (ii) dietary survey; (iii) physical and clinical survey; (iv) anthropological and social survey. Owing to the war the results of this investigation have not yet been published, but in a brief account given in an address to the Food and Nutrition Board at Washington in June 1943 I summarized some of the more interesting observations.

One example may be given to illustrate how indirect may be the attack required to improve nutrition. In one village studied it was found that on an average every woman spent over 4½ hours a day on four main tasks: pounding maize; carrying water; collecting and carrying wood; collecting materials for side dishes. All this was additional to any work done in the fields—and it must be realized that most of the agricultural work is done by the women—and to time spent on cooking, seasonal tasks like drying leaves, burning plants for potash, pot-making, grass-cutting for thatching, and mud-plastering of hut walls. Any attempt to improve nutrition must depend on the women who, in view of the time spent on such drudgery as the four tasks mentioned, have neither leisure to listen to instruction nor time to learn new ways.

The first step, then, in improving nutrition under such conditions would be the introduction of, say, a small stone mill in the village, and possibly the training of a miller to prepare meal from the staple grain. At once all the women would have a daily average of over 1½ hours to spare for new work. The cattle which, at the present time, are regarded merely as bank notes, might well be trained as draught animals to carry water. Trees in neighbouring tsetse fly-infested areas might be cut down and burned for charcoal to supply fuel. Opening up stream beds and conserving rainfall for irrigation would provide all the vegetables needed near at hand and save the time now spent on collecting greenstuffs from the bush.

Looked at in another way, the problem studied called for specialization in a community whose members were all Jacks-of-all-trades. Such a development would involve the establishment of secondary industries and the training of craftsmen. It might, therefore, be argued that the key to the solution is education: it might also be argued that this could best be done by developing the rudimentary apprentice system already existing, rather than by more academic methods of instruction.

This brief reference will serve to indicate how far it may be necessary to go in seeking a solution to a problem of nutrition, and how important it may be to make investigations on a broad basis. At the time when this work was done it seemed as if the survey was likely to be the best means of determining how to achieve good nutrition in a territory.

Planning for Nutrition

It is true that surveys of this kind still have their place but, as a result of experience gained during the war, my view is that emphasis should now be placed primarily on overall planning on a territorial basis (Platt, 1943).

In the first World War of 1914-1918, the *Royal Society* appointed a Food (War) Committee which examined various problems of nutrition and agricultural production in order to secure the best possible nutrition under war-time conditions. In the present war, in June 1940, the Lord Privy Seal, as Chairman of the Cabinet Committee on Food Policy, appointed the Scientific Food Policy Committee to "consider and advise upon the problems of national food requirements and of home food production with special regard to the shipping and foreign exchange likely to be available for imports of food and animal feeding stuffs and the labour and other resources likely to be available for home production" (International Labour Office, 1942). The results of the work of this body have not yet been published for security reasons, but it must be obvious that the problems in this war are essentially similar to those dealt with by the corresponding committee in the last one. The value of its work cannot be estimated without knowledge of it, but some of its fruits at the executive stage are in the hands of the Ministries of Food, Health, Agriculture and War Transport, and the report of the United Nations Conference on Food and Agriculture (1943a), quoting Great Britain as an example, stated: "Recent experience has demonstrated how effective a considered food and nutrition policy, based on scientific knowledge and experience, can be in safeguarding the health of a population."

In drawing up a scientific food policy the following steps are involved:

- i. Determination of the population's needs for health in terms of the more important nutrients: this includes knowledge of population-distribution in respect of infants, children, pregnant and nursing women and occupational groups, with selection of appropriate nutrient allowances. From these data the value for the per-person needs of the population can be calculated.
- ii. Translation of the nutritional requirements into terms of foods having regard to the customary foods of the people and the approximate amounts in which they are eaten.
- iii. The estimation of existing food supplies both from home production and from imports. It may also be necessary at this stage to consider potential as well as actual home production, taking into account its cost in terms of land and labour, and alternative sources of imports having regard to length of haul, etc., together with losses occurring in the handling and processing of foods, and the extent to which these might be reduced.

- iv. Comparison of the aggregate supply with the estimates of requirements based on nutritional needs, so as to detect and measure the gaps between the two and to determine how they should be filled.
- v. Arrangements for ensuring equitable distribution of the supplies of food available. In addition to an appreciation of the nutrition problem in terms of state of health, and to knowledge of food habits and customs and agricultural practices, a full understanding of the methods of distribution will be necessary as a basis for formulating nutritional policy in such a way as to secure the co-operation of the people, thereby strengthening the community socially as well as physically.

Some account of the results of this work on scientific planning of British war-time food policy has been given elsewhere in this *Bulletin*.^{*} The organization behind the formulation of the plans, which were carried out by the Ministries of Food, Health and Agriculture, involved the co-ordination of effort by statesmen at the highest level, with the assistance of scientific and technical advice covering a wide field of interests including medicine, agronomy and economics. In fact, the relationship between the scientific advisory body and the nation's Ministers was on a plan essentially similar to that described later in this essay. Much research work and technical investigation were undertaken in planning the nation's requirements under conditions of restricted food supply; one important example is to be found in the *Medical Research Council* (1940, 1941, 1943a) reports on the nutritive value of National Flour. Other enterprises, such as the production of B vitamins and protein by means of *Torula utilis* (Colonial Food Yeast Ltd., 1944) have not, in fact, been undertaken in Britain during the war, but may well prove to be of value in dietaries in other parts of the world in which supplies of these nutrients are unsatisfactory.

A considerable amount of work was carried out early in the war in instituting collective feeding schemes on a sound basis. Developments along these lines have led to a high standard of catering in various branches of the Armed Forces, and also in the control of feeding in industry. Illustrations of other special problems which have resulted in new knowledge and techniques are the design of compact rations for special troops, and guidance as to the best use of water and food supplies in lifeboats (*Medical Research Council*, 1943b).

Food planning in the United Kingdom, both in broad outline and in much of its detail, has been a war-time measure and owes its success largely to the misfortunes of war; will it be possible to extend this success into the peace? The United Nations Conference on Food and Agriculture (1943b) laid down all the plans necessary. Fundamental principles of food production are incorporated in such recommendations as the following (p. 23):

"That, as a first step in overcoming the general shortage of food, every effort should be made by countries whose agriculture can be expanded in the short-term period, so long as this is required and so far as the conditions of individual countries require or permit, to increase the acreage under crops for direct human consumption and even to hold back the rebuilding of depleted livestock herds—essential though this rebuilding will ultimately be—as well as the production of other crops which compete for acreage with essential foods." In regard to co-ordination, the Conference recognized (p. 24) that "it is essential for the preservation of life to secure, through equitable distribution, the maximum advantage from such supplies as may be made available"; and that the goal of governments and authorities should be the achievement of an economy of abundance.

Plans for the future made on a world scale would, in my opinion, have had a better hope of success had health as well as food and agriculture been taken into account. Recognition of the problems of malnutrition has been and always must be the concern of the medical man. No matter how many steps lie between recognition and the application of the remedy, the final assessment of its efficacy must again be a medical matter. How is this direction and co-ordination to be achieved?

The need for co-operation is summarized as follows in the report of the Committee on Nutrition in the Colonial Empire (1943, p. 168):

"A general and substantial improvement in nutrition in the Colonial Empire must depend upon the steady and concerted

^{*} [see BMB 492]

efforts over a period of years of many Government departments and voluntary agents. The primary responsibility necessarily rests with the Medical and Health Departments, but it is through the efforts of the Agricultural Department, working in conjunction with the Veterinary Department, that changes and adjustments in the production of foodstuffs must be made. Much can be done also by the Department of Education in contributing to an improvement in nutritional conditions. The efforts of the more specialized departments will not achieve their full effect unless they receive the support and co-operation of the Administration. Of equal importance is the need for securing co-ordination. Local nutrition committees should be capable of exercising an important influence in this direction, and we hope that they will continue as active bodies, and that full use will be made of their services."

I think that every community that can carry a nutrition council should have one, and that this council should appoint a technical panel or team consisting of persons from the departments of health, agronomy, education and administration. All members of the panel should possess special knowledge of nutrition and should have had field experience of both survey and development work in nutrition, in relation to their respective fields. It will probably be found necessary, in addition, to employ someone whole-time on nutrition work to act as co-ordinator of this body and its work, in council and in the field. I know of no better training for a team for this kind of work than to undertake a year's co-ordinated survey of the kind made under my direction in Nyasaland. By this means, I believe, the staff that will ultimately have to accept responsibility for the improvement of nutrition will, at the very outset, secure an appraisal of their nutrition problems which, with occasional expert assistance and advice, will enable them to plan and carry out plans. Their efforts should ultimately become an integral part of the routine work of their respective departments.

Research in the Future

What are the lines along which research in nutrition is likely to develop in the future? First, there will be day-to-day problems in medicine, food technology, sociology and economics associated with the formulation of nutrition policies. For example, in the Human Nutrition Research Unit, in food technology we have been working on a method of drying foodstuffs suitable for use on a small scale and in which food values and flavours are well conserved. In the medical field, work being done on the effects of nutritional and environmental factors on the healing of skin-wounds constitutes an attack on the problem of tropical ulcer. We have also explored the microbiology of the production of native African beers.

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In general, however, the tendency will be for fundamental work on nutrition to be in the associated sciences. There is a great deal to be done before we understand the function of the various nutrients in the body; no doubt in this connection the employment of new techniques, such as the use of marked atoms, will prove of great value. Again, the exploration of microbiological processes in nutrition of man and animals has scarcely begun, while our knowledge of plant physiology and biochemistry is scarcely more than rudimentary, and advances in these sciences must precede further significant advances in the chemistry of foodstuffs and their production. There will probably prove to be an important relationship between nutrition and the resistance to and recovery from zymotic disease of all kinds—a field hardly recognized. The interrelationship of the utilization of nutrients, and the production and function of endogenous substances such as the hormones, should also be further explored. Lastly, when there is no longer work to be done on the pathology of malnutrition, there is a field as wide as physiology itself in determining the effects of the supply of nutrients on the integration of physiological processes.

Conclusion

Although this outline of past and present trends of nutritional research and practice is an expression of the personal views and experiences of one worker, it reflects also the general development of the subject. At first the emphasis was on the study of major nutritional disorders. This conception of nutritional science as the identification and study of disease due to gross nutritional deficiency has now evolved through several stages to a deliberate planning of human society to ensure optimal nutrition. The beginnings of nutritional research were in medicine, agronomy, and the related sciences, and it seems probable that the present period of nutritional specialism will ultimately have served its purpose and will be followed by a resumption of the former division of responsibilities.

The practice of nutrition is now undergoing a phase of activity and popular interest. As newly acquired knowledge of microbiology at one time dominated various aspects of public-health work and claimed special attention in industry, so the practical application of nutritional knowledge is prominent in the present phase of development. In the course of time, however, with continued demonstration of the benefits which must accrue from world-wide attainment of good nutrition, with ever-widening diffusion of knowledge of its principles, and with trained personnel working under the ægis of responsible agencies, the practice of nutrition will in its turn cease to occupy so prominent a position and will emerge into the ordinary routine work of these agencies.

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¹ [see BMB 493]

PROTEIN METABOLISM

D. P. CUTHBERTSON, M.D., D.Sc.

Member of Staff, Medical Research Council

The organic matrix of the body is essentially protein in nature and protein also plays an important part in the osmotic relationships of the body fluids and in the nutrition and regulation of the cells which these fluids bathe. Although

seeming to play a static role, there is nevertheless in this matrix a dynamic equilibrium between the protein constituents and the amino-acids which are present in the body fluids.

The number of proteins is very large, yet they are all constructed of relatively few units—the amino-acids—whose number is about equal to the letters of the alphabet, but whose position and preponderance in the protein varies with each protein and gives to it its peculiar properties. These amino-acids have an extraordinary facility for being joined in chains, as it were head to tail, by means of peptide linkages. These chains, and there may be as many as 16 component chains, seem usually to be rolled up so as to take on a globular or ellipsoidal shape: exceptions are the long fibrous proteins like hair.

The process of digestion provides the organism with the building stones—*Bausteine*—for the creation of its own tissue proteins. The products of enzymic hydrolysis do not necessarily conform to the body's requirements but further transmutations take place to meet this defect and also to meet the requirements of the moment. Two of these will first be considered.

Protein Transmutation

Transamination: Protein has been said to contain the magic of life: ever newly created, ever dying. The truth of this has received considerable emphasis from the work of the two Russian biochemists, Braunstein & Kritzman (1937). They described this process of "transamination", which is a shuttle mechanism that enables the cells to change keto-acids to amino-acids by replacing the oxygen atom of the ketone with NH_2 transferred from the $\text{CH}(\text{NH}_2)$ of either of the dicarboxylic acids, aspartic or glutamic, to the CO group of the ketonic acid. By partial oxidation of carbohydrates, some at least of the keto-acids can be produced, and in the process of transamination we have a means by which the body can form a portion of its amino-acids. The muscles are particularly rich in the enzyme which brings this about. An excellent review of this special mechanism has been published by Cohen (1942).

Transmethylation: It was du Vigneaud and his co-workers (1939, 1940) who first postulated and later gave direct proof that methyl groups can be transferred from methionine to other substances in the body. They identified choline in the vitamin-B complex as being capable of being formed from methionine with the aid of methyl groups. They administered methionine of which the methyl group was marked by having one of its hydrogen atoms replaced by deuterium. When this "labelled" methionine was fed to rats on a choline-free diet, choline could be isolated from their tissues with part of its methyl groups containing the deuterium. Du Vigneaud, John, Chandler, Schenck & Simmonds (1941) also found at this marked methyl group could be transferred from choline to creatine. The methyl group of methionine could therefore be used by the body to synthesize two of its essential α -amino-nitrogenous constituents. The transfer of methyl groups from methionine to creatine was demonstrated by Borsook & Dubnoff (1940).

The brilliant work of the late Dr. Schoenheimer and his colleagues over a number of years has, more than anything else, demonstrated the extent to which nitrogen fed in the form of amino-acids is synthesized into tissue proteins, both in the form of the fed amino-acids and of other amino-acids to which the nitrogen is transferred by transamination. In these experiments they have used heavy nitrogen (N^{15}), deuterium and radioactive carbon. They have found that every protein in the body is continually changing and renewing its structure. By the use of these isotopes they have shed new light on some of the most hidden mysteries of intermediary metabolism. (In 1942 Schoenheimer and Ratner reviewed their work in relation to protein metabolism. Numerous papers from Schoenheimer's department have appeared since in the *Journal of Biological Chemistry*.)

In many other directions considerable progress has recently been made in our understanding of the physiology and pathology of protein metabolism. Some of these will now be considered.

Protein and Amino-Acid Requirements

The main function of protein in the diet is the provision of nitrogen and sulphur in the form of amino-acids for growth, maintenance, reproduction, lactation, repair and convalescence. Some proteins are also a valuable source of phosphorus. In recent years, with improved analytical methods, the centre of interest has been shifting from the proteins themselves to their constituent amino-acids, and the urgent

problem in this field is the determination of the amino-acid requirements for man in health and disease.

The task of finding which of the 22 amino-acids are indispensable parts of the diet, and which the animal body can build for itself, has exercised the attention of many leading biochemists. The names of Hopkins, Mendel, Osborne and Rose are especially associated with this field of work. Rose (1938) was able to divide the amino-acids into two groups according to whether they need or need not be supplied in the diet of the growing rat. The amino-acids which were found to be indispensable in the diet were lysine, tryptophane, phenylalanine, leucine, isoleucine, threonine, methionine, valine, histidine and arginine.

These results Rose afterwards confirmed in the dog, and later Bauer & Berg (1943) confirmed them in the mouse. The qualitative requirements having been worked out, further tests demonstrated the approximate percentage of each of these amino-acids which must be included in the diet to produce the maximum rate of growth of the rat.

For the maintenance of nitrogen equilibrium, histidine and arginine did not appear to be essential. Methionine, if sub-optimal in amount, could be supplemented by cystine for growth-promotion, and the same relationship might exist between phenylalanine and tyrosine.

Burroughs, Burroughs & Mitchell (1940) and Mitchell (1942), from a study of the maintenance of the adult rat, came to the conclusion that lysine, leucine, histidine and arginine were not necessary and that tyrosine could apparently replace phenylalanine. Norleucine appeared to be able to function by promoting the synthesis of lysine or leucine or both. These workers came to the conclusion that for maintaining nitrogen balance in the adult rat the following amino-acids were required: threonine, isoleucine, leucine or norleucine, tryptophane, valine, and methionine. The authors consider that only in growth does *total* protein synthesis occur, while in the adult animal only "particular requirements" must be met.

Within the last year or two, Rose has been able to accumulate sufficient of the amino-acids found essential for the growing rat to make human trials possible. No one has yet ventured to determine the growth requirements of the child, but studies on adult men are now in progress. So far, it appears probable that what was found necessary for the rat will also be found qualitatively necessary for the human, and the non-essentiality of the 12 amino-acids which were found dispensable for the rat applies also in man. The essentiality of valine, without which there is a profound and immediate negative balance, methionine, threonine, leucine, isoleucine, and phenylalanine, have already been confirmed. Removal of histidine produced no disturbance of nitrogen equilibrium, indicating its apparent non-essentiality for maintenance (Rose, Haines, Johnson & Warner, 1943). Albanese *et al.* (1941, 1943a, b) and Holt *et al.* (1941, 1942) have also studied the effects of the following deficiencies in man: tryptophane, lysine, arginine, methionine and cystine. They found that when arginine was removed from the diet a reduction in the number of spermatozoa in the seminal plasma took place.

Madden, Carter, Kattus, Miller & Whipple (1943) have found that the 10 amino-acids found adequate for growth when tested on standardized plasma-depleted dogs produced new plasma protein in abundance. It was found that methionine could not be replaced by cystine without affecting the other tissues. Although not required for nitrogen balance for as long as 1 to 2 weeks, arginine was required in the diet of the plasma-depleted dog for plasma-protein formation. It is of interest that the glycine requirements of the chick are so high that glycine becomes an essential amino-acid (Almquist, 1942).

Attempts have recently been made to determine the specific effects of single amino-acid deficiencies. The work of Harris, Neuberger & Sanger (1943) indicates that as the result of lysine deficiency cessation of growth and hypoproteinaemia develop in young rats. The number of erythrocytes and the amount of haemoglobin per unit volume of blood are slightly lower than in the control animals. These changes are believed to indicate a retarded development of the haemopoietic system. Radiologically the deficient animals exhibit a decrease in subcutaneous fat, muscle-wasting, and reduction of calcification in the bones. The epiphyseal cartilage in the long bones is barely visible and there is histological evidence of a reduction in the number of chondroblasts in the first zone of proliferating cartilage. Mitosis

appears to be reduced in the testes. This deficiency leads to a general inhibition of protein formation and protein is transferred, e.g. from muscle, according to a fixed system of priorities—the body-weight remaining fairly constant and the effect being similar to partial starvation.

One of the difficulties in testing the effects of deficiency is the effect that the deficiency often has on appetite. Paired feeding controls eliminate this difficulty to some extent, although it may be argued that any decline in appetite is part of the symptom-complex of the deficiency.

Albanese & Irby (1943) have brought forward some indirect and not very convincing evidence that the unnatural (*d*-) forms of certain of the amino-acids which cannot be utilized may have a toxic effect. Kinsey & Grant (1944) have found no evidence of this in the rat, in spite of using racemic mixtures of isoleucine, methionine, phenylalanine, threonine, tryptophane and valine, and no evidence of toxicity has emerged from human trials. The *d*- and *l*-forms of methionine are both utilized. The metabolic fate of the unnatural form of the others is largely unknown, but it is generally believed that they are not utilizable.

Methionine as a precursor of cystine plays a very important role in the formation of the scleroproteins of the epidermal structure and also of certain hormones, particularly insulin. Phenylalanine presumably furnishes the nucleus for the synthesis of thyroxine and of epinephrin. Arginine is considered to supply the amidine group for the synthesis of creatine (Block & Schoenheimer, 1941).

Melnick (1943) gives interesting data on the composition of the average daily American diet per capita in terms of essential amino-acids. As the methods of analysis for certain amino-acids are still very difficult and uncertain, too much stress should not be laid on the accuracy of these figures which are: lysine, 5.1 g.; tryptophane, 1.1 g.; phenylalanine,¹ 4.3 g. (tyrosine, 3.8 g.); leucine, 10.7 g.; isoleucine, 3.3 g.; threonine, 3.4 g.; methionine,¹ 2.8 g. (cystine, 1.2 g.); valine, 4.2 g.; histidine, 1.8 g. and arginine, 4.8 g. This accounts for about half the total amino-acids in the diet.

Block & Bolling (1944) have also discussed the amino-acid constitution of different proteins and their ability to furnish the essential amino-acids, and the following salient points are taken from their paper.

Human milk proteins yield significantly more arginine, tryptophane and cystine plus methionine than cow's milk. Human milk appears also to be richer in isoleucine. It is considered that the proteins in milk are so constituted that the infant can form the maximum quantity of new tissue from the minimal amount of ingested protein.

It is suggested that the best way to enable the organism to replenish its blood proteins after extensive loss would be to supply histidine, lysine and threonine, as they are high in blood proteins when calculated on the basis of two-thirds haemoglobin to one-third serum proteins. Blood proteins have low contents of cystine, methionine, and isoleucine.

Egg proteins are decidedly higher in arginine and the S-amino-acids than milk and blood. The formation of these proteins is probably concerned with the high requirement of the growing chick for these amino-acids.

There do not seem to be any marked differences between the meat- and fish-muscle proteins, with the possible exception of the lysine content, which may be significantly higher in meat proteins. Meat yields more lysine but less tryptophane and cystine than does egg. The small quantity of these last two amino-acids in meat proteins may account for their lower nutritive value as compared with egg proteins. Meat is a superior source of arginine, methionine and probably cystine but inferior as a source of the aromatic acids. Gelatin is deficient in, or almost devoid of, histidine, tyrosine, tryptophane, phenylalanine, cystine, methionine, threonine, leucine, isoleucine and valine.

Maize (corn) proteins may be richer in tyrosine, methionine, leucine and valine but poorer in tryptophane and possibly in phenylalanine than those of wheat. With regard to the proteins of the germ or embryo, those of maize appear to be a better source of all the aromatic amino-acids as well as of those of the leucine group. Both maize- and wheat-grown proteins are well balanced with respect to their essen-

tial amino-acids and compare favourably with the common proteins of animal origin. The nutritive values of milk and maize proteins are approximately equivalent for purposes of growth, and the addition of either to the proteins of refined wheat flour resulted in a marked increase in the growth-promoting ability of the diet. Maize gluten yields less histidine, lysine, tryptophane, and glycine, but more tyrosine, methionine, leucine, isoleucine, and valine, than wheat gluten. The easiest way to improve the nutritive value of wheat gluten is to incorporate lysine or a lysine-concentrate into the flour.

Cottonseed, linseed, and peanut yield adequate quantities of arginine and histidine, but only one-third to one-half of the lysine furnished by most edible animal proteins. Linseed meal appears to be rich in tryptophane, being equal to or apparently better than milk. Cottonseed and peanut proteins are rather low in methionine and threonine, but higher in valine than any natural food considered in the paper under discussion.

Although yeasts appear to furnish proteins superior even to soya beans, the balance of the essential amino-acids in both these foodstuffs is generally satisfactory, except for the mild deficiency in methionine. By the inclusion of whole corn or corn gluten in the diet, or possibly the addition of a small quantity of cystine, this lack can be corrected, as the lecithin present in whole soya beans should provide an ample quantity of methyl groups in the form of choline.

Meats and fish furnish half the lysine intake even though they account for only 38 % of the total protein. Meats and fish are also superior sources of arginine and threonine. The presence of collagen in meat will tend to decrease cystine, methionine, tyrosine, tryptophane and threonine, and increase arginine and especially glycine.

If the freely selected mixed diet in America during 1937–41 be taken as representing a suitable intake of amino-acids, then eggs are the only single article of diet which supply the essential amino-acids in truly balanced proportions.

It does not appear that soya beans, peanuts, etc. can fill the void created by the marked deficiency in lysine of the cereal grains. Although cereals are consumed to the extent of 27 % of the total protein of the diet they furnish only 10 % of the lysine.

Studies on a low economic group made in Spain (Robinson, Janney & Grande Covián, 1941) have shown that in spite of an apparently adequate intake of total protein (66 ± 2.7 g. per day) and of iron (11.4 ± 0.43 mg. per day), one-sixth of the group exhibited dyscrasias which may possibly have been directly attributable to a deficient consumption of lysine since the intake of animal protein was 22 ± 1.7 g.

If the sole source of energy and protein were bread, it would be necessary to consume approximately $6\frac{1}{2}$ pounds [about 3 kg.] daily for optimal amino-acid intake. However, if either (a) 2 g. lysine per 100 g. protein is added to bread made with $6\frac{1}{2}$ % milk solids, or (b) 3 g. lysine per 100 g. protein is added to bread without milk solids, the average daily requirement for the essential amino-acids would be met by consumption of only 108 g. protein in the form of approximately 3,600 calories (equivalent to slightly more than $2\frac{1}{2}$ pounds of bread).

A few years before the war Boas Fixsen (1935) reviewed the whole field of the biological values of proteins. During the war, British work on this subject has naturally turned to the proteins of wheat flour submitted to different degrees of extraction and also to previously unexplored sources of protein, in the hope that some unusual protein of high biological value might come to light which would compensate for the shrinkage in animal protein which appeared imminent.

Chick (1942) found that the proteins of *National Wheatmeal* (85%-extraction) flour had an advantage over the proteins of white flour (75 % extraction) of 13 % to 16 % extraction, and that the biological value of the proteins of whole wheatmeal was even higher, namely 17 % to 26 %. The calculated coefficients of digestibility of the proteins of wholemeal and *National Wheatmeal* flours were lower than that of white flour by 6 % and 3 % respectively, losses which were more than compensated by the greater nutritive value of these flours.

It has recently been found that the non-protein nitrogenous constituents of expressed potato juice contain some substance(s) which so complement the amino-acids of the protein of the potato as to produce a mixture of biological value equal to that of the protein itself (Chick & Cutting, 1943).

¹ [Phenylalanine is the essential amino-acid from which the body can form tyrosine. As tyrosine is required for certain specific purposes—e.g. thyroxine synthesis—the presence of dietary tyrosine reduces the dietary requirement of phenylalanine. There is a similar relation between methionine and cystine.]

Pirie (1942) has suggested that under certain circumstances, the conversion of part of the protein of leaves into human food could be more effectively performed by industrial chemical methods and equipment than through the ruminant. Although adequate feeding experiments with leaf proteins have not yet been made, the available data on amino-acid composition and early feeding experiments with dried leaves suggest that such a protein is of high biological value. Grass, lucerne and cabbage are considered the best sources. It is estimated that 200 pounds [about 90 kg.] of leaf-protein N could be harvested from one acre [about 4,000 m.²] each year, and Pirie has suggested that research should be devoted to the maintenance of a supply of leaf material of high N content during several months of the year, and to the design of a suitable macerating plant.

As revealed by the Report on Food Consumption Levels, the protein available per head per day of the civilian population in the United Kingdom did not fall below 80 g. (36 g. animal) even in 1940 (Ministry of Food, 1944).

Interest has been developing in the determination of the biological values of the proteins of a mixed dietary and Macrae, Henry & Kon (1943) have recently determined the biological value of the mixed proteins of the diet served at four *Royal Air Force* stations, as determined by Mitchell's method. They found values of 77.7 to 81.2—which are surpassed only by the proteins of eggs and milk. This observation indicates that the process of amino-acid supplementation which takes place in a normal diet is effective in compensating for the varying deficiencies of the individual proteins composing it.

Even non-essential amino-acids and incomplete proteins have a nutritional value, and the latter may supplement the value of proteins of higher biological efficiency than they themselves possess. Although much work still remains to be done in assessing the biological values of the mixed proteins of different protein-containing foodstuffs, more attention must be directed to determining the amino-acid composition of these proteins. Once this is accomplished and our requirements for the essential amino-acids are known, it will be possible to predict the biological value of a protein or mixture of proteins from its amino-acid constitution.

Microbiological assay methods for amino-acids: The discovery by Mueller & Cohen (1937) that β -alanine is an essential growth factor for the diphtheria bacillus has provided a microbiological assay method for this compound. Recently a number of papers have appeared dealing with the microbiological determination of amino-acids using cultures of *Lactobacillus arabinosus* (Kuiken, Norman, Lyman & Hale, 1943; Shankman, Dunn & Rubin, 1943a, 1943b; McMahan & Snell, 1944) and of *Lactobacillus casei* (Shankman, Dunn & Rubin, 1943b; McMahan & Snell, 1944). By omitting one of the amino-acids essential for the growth of these organisms, a medium for the estimation of that particular amino-acid is prepared, titration of the amount of lactic acid formed in the test culture being indicative of the amino-acid which is present in the unknown. This method is useful for estimating the presence of some 11 amino-acids in hydrolysates from less than 1 mg. protein, including valine, leucine and isoleucine, which are difficult to estimate chemically.

Protein in relation to mineral metabolism: McCance, Widdowson & Lehmann (1942) have recently reported studies which show that in the adult subject periods of high protein intake induced high net absorptions of calcium and high urinary calcium outputs. The retentions of magnesium were greater in the high protein period and again there was a higher urinary output as compared with a low protein diet. There was also evidence of a slight beneficial effect on phosphorus but little effect on iron absorption. It is suggested by the authors that very little calcium would be absorbed if the diet contained no protein or amino-acids.

Linneweh & Shobin (1940) found evidence in plasma-depleted dogs that there occurred a definite, simultaneous, and parallel reduction in total protein, albumin and globulin and in the total and ultrafiltrable calcium. After intravenous administration of calcium, either the serum calcium and the protein levels were raised or the fall was prevented, again in parallel. In cases of hunger-œdema, eczema and severe anaemia studied, the calcium level of the blood rose with the protein level. These workers therefore concluded that the calcium level of the blood is not entirely regulated by hor-

mones or vitamins, but that it is, partially at least, a function of the protein level.

Quantitative requirements of protein: For the more quantitative aspects of protein nutrition the reader is referred to the reviews which appeared in *Nutrition Abstracts and Reviews* during the period 1936–40, by Garry & Stiven (1936) on the requirements in pregnancy and lactation, by Leitch & Duckworth (1937) on the determination of the protein requirement, and by Cuthbertson (1940) on the quality and quantity of protein in relation to health and disease. Since its inception in 1932 there have been admirable summaries on the biochemistry of the proteins and the amino-acids, and also on nutrition, in *Annual Review of Biochemistry*.

In 1941 the Committee on Food and Nutrition of the U.S.A. *National Research Council* recommended daily allowances of protein according to age, sex and level of activity. The writer has revised these in terms to suit the dietary habits in the United Kingdom (Cuthbertson, 1944a) [see table].

TABLE
COMPARISON OF AMERICAN ALLOWANCES OF CALORIES AND PROTEIN (N.R.C. STANDARDS) WITH VALUES REVISED TO SUIT DIETARY HABITS IN THE UNITED KINGDOM

	American allowances			Revised (net values)		
	calories	protein g.	% of calories derived from protein	calories	protein g.	% of calories derived from protein
	70 kg.			61 kg.		
<i>Man</i>						
moderately active	3000	70	9.6	2900	75	10.6
very active	4500	70	6.4	4200	110	10.7
sedentary	2500	70	11.5	2400	65	11.1
<i>Woman (56 kg.)</i>						
moderately active	2500	60	9.8	2500	65	10.7
very active	3000	60	8.2	3200	80	10.3
sedentary	2100	60	11.7	2100	55	10.7
<i>Pregnancy (latter half)</i>	2500	85	13.9	2500	75	12.3
<i>Lactation</i>	3000	100	13.7	3000	95	13.0
<i>Children up to 12 years</i>						
1 to 3 years	1200	40	13.7	1200	40	13.7
4 to 6 years	1600	50	12.8	1600	50	12.8
7 to 9 years	2000	60	12.3	2000	65	13.3
10 to 12 years	2500	70	11.5	2500	80	13.1
<i>Children over 12 years</i>						
girls { 13–15 years	2800	80	11.7	2800	90	13.2
{ 16–20 years	2400	75	12.8	2400	70	12.0
boys { 13–15 years	3200	85	10.9	3200	100	12.8
{ 16–20 years	3800	100	10.8	3800	110	11.9

Protein Intake in Relation to Energy Expenditure, Muscle Work, Physique and Resistance to Disease

Energy expenditure: The present writer, as the result of an earlier survey of the literature (Cuthbertson, 1940), came to the following conclusions:

- i. In its capacity to supply energy, protein is apparently no more useful than carbohydrate or fat, except by virtue of its specific dynamic action which makes it particularly suitable for those exposed to cold. This action, and other evidence as to the economic bodily use and storage of protein, strongly suggest that the digestion of protein should not be dissociated in time from the digestion of carbohydrate. The more perfectly balanced a diet, the greater is the efficiency with which protein is utilized and the less will be the wastage as heat.
- ii. Man can apparently adjust himself to greatly varying levels of protein intake, and the protein may be exclusively animal or vegetable in origin, or of any intermediate mixture, no deleterious effects resulting from either extreme, provided the process of amino-acid supplementation is effective to cover the requirements of the individual essential amino-acids, and the total intake is adequate.
- iii. The level of protein intake for any particular population, when expressed as a percentage of the total calories,

tends to remain constant at all grades of muscular activity with, perhaps, the exception of athletes training for special events, who in general select diets containing a higher proportion of protein, chiefly of animal origin. It is not clear what purpose this increased protein intake serves. Unless the diet contains a very high proportion of sugar, highly processed cereals, and fat, it is difficult to plan a diet providing less than 10 % of its calories as protein. Most diets, with the exception of those of some highly carnivorous races and tribes, have 10-14 % of their calories as protein.

iv. In general, it may be said that whenever and wherever economic circumstances permit, man elects to raise his intake of animal protein to the region of 60 % of the total protein.

Howe has recently (1942) provided details of the optimal dietaries planned for the U.S. soldier in training. These contain 120 g. protein and some 4,000 or more calories. This protein value works out at 12 % of the calories.

Muscle work : On the difficult question of the role of protein in muscle work, Gemmill (1942) has concluded from his survey of relevant literature that the use of carbohydrate is of primary importance, but that long-continued work produces an increase in the output of nitrogen in the urine which, however, bears no direct relationship to the work done. It is postulated that when exercise reduces the carbohydrate supply of the body, extra protein is deaminized to supply carbohydrate or carbohydrate intermediates. The evidence for this assumption is based on the observation that ingestion of carbohydrate abolishes the increment of nitrogen output. This viewpoint is in agreement with the earlier evidence of the present writer and his colleagues (Cuthbertson, McGirr & Munro. 1937).

Resistance to fatigue : The history of the use of glycine and gelatin (which contains 25 % glycine) in the treatment of muscular dystrophy and in relation to resistance to fatigue has recently been reviewed by King, McCaleb, Kennedy & Klumpp (1942), Beard (1943) and Keys (1943). The evidence is very conflicting and the case for glycine, on the balance of evidence, is "not proven." Beard believes that to demonstrate the effect of glycine it must be given in adequate amounts, e.g. 12 g. per day on a normal or high protein diet, and must be given for well over three weeks, as he found that the first increases occur after that period. He considers that if enhanced muscular performance has already occurred as a result of training, it is impossible to expect any additional substance to increase the work output.

Physique : From a survey of the diets of the peoples of the earth, it appears, in general, that those races having a fairly high protein intake, especially animal protein, are more virile, robust and energetic and have better physiques. It also appears that there is less active tuberculosis in races or groups with such a diet, but it is not proved that the increased resistance or physical well-being is due to protein itself or to an accompanying superior diet (Cuthbertson, 1940).

Immunity : In the field of immunity the evidence is fairly conclusive that an antibody is a molecule of globulin which, during synthesis, has been specifically modified under the influence of antigen. By the use of isotopic amino-acids it was found that the uptake of dietary nitrogen which accompanies body-protein synthesis, through amino-acid replacement and nitrogen transfer among individual amino-acids, was also shared by the antibody protein which is formed when isotopic amino-acids are administered to actively immune rats and rabbits (Schoenheimer *et al.*, 1942b). Antibody formation during active immunity appears to be a continuous process of production and shares in "labelled" N^{15} which has been added to the diet. On the other hand, passive antibody formation during passive immunity appears to have little relation to dietary N (Heidelberger *et al.*, 1942).

How far the antibody formation plays a really significant rôle as a competitor for the available amino-acids in protein under-nutrition is perhaps difficult to conceive, as the total amount required in proportion to the tissue proteins must be very small indeed. Nevertheless, probably just because there is so much competition for the available amino-acids in the under-nourished subject, antibody formation may share in the general restriction in protein anabolism.

Attention may also be drawn to the well-known tendency of marasmic infants to die of intercurrent infection, the great susceptibility of patients with nutritional oedema to respiratory and other infection, the terminal infections in malignant

renal or hepatic diseases, and the general rise in death rates from tuberculosis and other infectious diseases in war time. The concomitant occurrence of hypoproteinaemia and an increased susceptibility to infection suggests the possibility of a mutual relationship. Animals made hypoproteinaemic manifest a definite loss of ability to produce antibodies of several kinds (agglutinins, precipitins, hæmolysins). The loss of acquired immunity is manifested particularly in diseases characterized by a marked protein deficiency. This aspect of the literature has recently been reviewed by Cannon (1944).

Nuclear and Cytoplasmic Proteins

The recent work on the importance of the nucleic acids and nucleoproteins in animal tissues, particularly in connection with cellular activity, has suggested that nucleoproteins containing pentose nucleic acids ("ribonucleoproteins") play a special rôle in protein synthesis and tissue growth. It is now known that the nucleoproteins containing these nucleic acids are constituents of many self-reproducing filterable viruses, and they appear to be abundant in the rapidly growing cells of embryos, tumours, and regenerating tissues. Mirsky (1943) and Davidson & Waymouth (1944c), who themselves have contributed much of value in this field, have recently reviewed the evidence for the essential rôle of nucleic acids in nuclear structure and for the association of nucleoprotein and nucleic acids with the processes of growth. The evidence suggests that rapidly-growing embryonic tissues are characterized by both a high nuclear desoxyribopolynucleotide content and a high cytoplasmic ribopolynucleotide content (Davidson & Waymouth, 1943; 1944a; 1944b).

A new conception of the chemistry of the nucleus has been opened by the discovery of a new nuclear protein "chromosomin" by Stedman & Stedman (1943a, 1943b, 1943c, 1944). This protein has predominantly acidic properties and is believed to be one of the principal components of the chromosomes.

Protein in Relation to the Function of Organs

Kidney : While over-eating in general seems definitely to be connected with arterial hypertension, there appears to be no real evidence for the belief that high-protein diets lead to nephritis and hypertension. Indeed, the general trend of work is to show the beneficial effects in some types of nephritis, particularly where oedema is present, and also in the toxæmias of pregnancy, of diets containing considerable amounts of protein daily. This high protein intake has a diuretic effect due to the amount of urea formed, and this assists in bringing oedema under control (Cuthbertson, 1940).

Recently attempts to test the effect of a high-protein diet on the organism with impaired renal efficiency, have been made on the dog by Philipsborn, Katz & Rodbard (1941). They found that no rise in blood-pressure resulted from the imposition of a high-protein diet in dogs with normal blood-pressure but with their renal arteries subjected to temporary total or chronic partial occlusion. Again, in animals with moderate hypertension and slight renal insufficiency, no rise was noted. It was only in some of the animals with moderate renal insufficiency and frank hypertension that an effect was observed. Guerrant, Scott & Wood (1943) also found that no consistent rise or fall in systolic or diastolic blood-pressure occurred in normal dogs, or in hypertensive dogs fed on a high-protein diet of lean raw meat for long or short periods, the hypertension being produced by partial occlusion of first one then the other of the renal arteries.

It has now been found that urinary protein is either entirely serum albumin or a mixture represented by the albumin : globulin ratio as found in the urine. The urinary protein of a nephritic was not altered by changing from an egg-free to an egg diet (Murrill, Block & Newburgh, 1940).

In Bright's disease, two changes of plasma amino-acid content in opposite directions have been noted in Van Slyke's laboratory (Van Slyke, 1942). One of them was discovered by Kirk in patients in or near uræmic coma. The plasma amino-acid level in some of these patients rose in a day or two from little above the normal level to six- or eight-fold as much. If recovery occurred, the plasma amino-acid level fell as quickly to normal. How far the sudden rise is due to an accelerated tissue-breakdown accompanied by a simultaneous failure of the liver to deaminate is a matter for conjecture, as the mechanism remains unknown.

In the opposite direction, Farr & MacFadyen (1940) found

that the plasma amino-acid level was below normal in the nephrotic type of Bright's disease and that recovery corresponded to a rise to normal levels. Acute clinical manifestations, "nephrotic crises," became apparent when the level fell to 2.5 mg. or lower per 100 ml. When 33-57 % of the dietary nitrogen of nephrotic children was replaced by a casein hydrolysate given intravenously, neither the course of the nephrotic disease nor its ultimate outcome was affected. For this reason the use of such a hydrolysate to treat the hypoproteinaemia of the nephrotic is not advocated by the authors. It is believed, however, that a positive bloodstream infection in nephrotic patients is a definite indication for intravenous amino-acid therapy.

It is not proposed to discuss here the rather academic researches which relate kidney hypertrophy to the presence of the excess of certain amino-acids in the diet.

Liver: A discussion on the relation of the liver to protein metabolism would occupy a monograph by itself. There are, however, certain aspects which are worth noting in passing. The first relates to the inter-relationship of certain amino-acids to the nutritive condition of the liver, methionine and cysteine in particular.

Miller & Whipple (1942) have recently demonstrated in the protein-depleted dog that methionine, if given shortly before chloroform anaesthesia, provides complete protection against hepatic damage, and that this amino-acid, or cysteine + choline, gives significant protection even if administered 3 to 4 hours after chloroform anaesthesia. After 4 hours no protection was provided. Choline itself did not give protection beforehand. The livers of these protein-depleted animals were deficient in both N and S, the latter in particular. Administration of methionine or cysteine promptly made good this deficit.

These investigators, on the basis of this protective action of methionine (e.g. casein), or of various proteins by mouth or vein, suggest their use as therapeutic agents where there is any type of damage to the liver or other organs. Methionine in solution can be administered parenterally or with glucose, without any unfavourable reaction in man and animals. It had previously been suggested by Miller, Ross & Whipple (1940) that chloroform, by combining with the sulphhydryl groups, may inactivate enzyme systems unless there is an adequate reserve of these groups.

Supplements of methionine, cystine or cysteine, especially the last, largely prevented the marked inhibition of growth in young rats fed on an 18 % casein diet containing 0.12 % cobaltous sulphate. The high mortality due to oral or intraperitoneal administration of very toxic levels of cobalt or nickel was also prevented by the simultaneous and separate administration of cysteine. The complex formed between cobalt and cysteine *in vitro* was relatively non-toxic, suggesting that cobalt poisoning is due to the fixation and loss of sulphhydryl compounds in the tissues.

Messinger & Hawkins (1940) found that protein was the most effective dietary principle in protecting dogs against arsphenamine liver injury. On a protein diet the damage was trivial and was rapidly repaired. Carbohydrate was not uniformly so successful: fat was definitely deleterious to the dogs.

Probably even more important than its effect on susceptibility to known toxic agents, is the direct necrotizing effect on the liver of methionine deficiency alone. Depending upon the degree of the deficiency, changes in the rat's liver ranging from fatal acute yellow atrophy to a variety of chronic hepatic cirrhosis have been produced by Himsworth & Glynn (1944) in animals given a low-protein diet. The determining factor is the amount, quality and quantity of protein eaten. Casein, even in small amounts, protects against the lesion, while yeast protein even in liberal amounts fails to protect. These investigators have found that complete protection can be provided by methionine—an amino-acid in which casein is particularly rich. They put forward reasons for believing that, in man, massive hepatic necrosis and its sequel nodular hyperplasia may be attributed to a trophopathic hepatitis, and that, whatever the nature of the primary illness, this massive hepatic necrosis is to be regarded as a conditioned deficiency disease. The action of many so-called liver poisons, e.g. trinitrotoluol, cinchophen and neoarsphenamine, is believed to be brought about by their interference with methionine in the body.

Beattie & Marshall (1944) have published their preliminary results based on a study of 450 cases of infective hepatitis

and "post-arsphenamine" jaundice. These would appear to indicate a beneficial effect of the methionine and of casein digests rich in methionine. "In gravely ill patients, the results obtained by methionine treatment have been so striking as to leave no doubt as to the efficiency of the treatment, especially in those cases which have remained jaundiced for weeks or months and were in a state of icterus gravis when methionine was initiated." The addition of cystine is believed by the authors to spare the methionine. That caution should be exercised before accepting their findings as revolutionizing treatment is evidenced by the note by Peters, Thompson, King, Williams & Nicol (1944), which appeared shortly after Beattie & Marshall's report. Peters *et al.* have now studied more than 450 cases of "post-arsphenamine" jaundice and have found that methionine and also cystine had a significant but not remarkable effect on the course of the jaundice. Casein, equivalent in methionine content to that administered separately, was found to have no action. This could not be explained. While it is quite conceivable that there may be a fixation of arsenic through sulphhydryl compounds, there is as yet no reason to believe that these compounds should be of benefit in infective hepatitis, the aetiology of which is completely unknown.

Choline prevents and cures fatty liver in rats and for this reason was called a "lipotropic" substance. Deficiency of choline appears to lead to a deficiency of the compounds concerned in lipid transport, and renal haemorrhage may occur at a critical period when there is an acute shortage of essential cellular materials. Betaine, methionine and other substances may also be regarded as lipotropic. For diets free of choline, betaine, methionine and other lipotropic factors, it is suggested that the term "alipotropic" should be used, and for the effects of cystine, cholesterol and other substances with similar action in this sense it is considered that the term "antilipotropic" would be appropriate.

Recent work on arsenocholine has shown that this compound behaves in a similar fashion to choline in its lipotropic action and in preventing and curing acute haemorrhagic effects. Arsenocholine appears to be utilized intact in the biosynthesis of lecithin. It is completely inactive as a methyl donor, and this suggests that choline exerts its effects through reactions involving the intact molecule. Previous theories on the lipotropic activity of choline, betaine and methionine had been based on their possession of a labile methyl group. By using radio-active phosphorus and heavy nitrogen it has been shown that choline and other lipotropic factors accelerate the elimination of phospholipids in the liver and other tissues; the most active seat of change being the former.

Ethanolamine is the generally accepted precursor of choline. The choline content of the body is dependent to a limited extent only upon the amount of choline in the diet, the level being maintained by methylation. The source of liver fat in the alipotropic diets appears to be mainly dietary fat or dietary carbohydrate.

The anti-haemorrhagic action of choline, betaine and methionine seems to parallel their lipotropic effect. Cystine and cholesterol may counteract both effects. The rate of phospholipid turnover in the kidney is accelerated by choline but to a less extent than occurs in the liver. The anti-haemorrhagic action is probably general but varies in degree with the different tissues.

Choline naturally promotes the growth of young rats subsisting on a relatively alipotropic diet. It can also accelerate growth when added to an alipotropic diet containing homocystine. The latter is neither lipotropic nor growth-promoting. Methionine is produced from homocystine by utilization of the methyl groups of choline. Homocystine, however, is not a natural product.

The literature on this subject is considerable but has been reviewed by Best & Lucas (1943) who hold that some international group should decide whether to call choline simply a dietary factor (as the authors term it), or a vitamin (as György would term it), or a vitagen (according to Rosenberg). From the metabolic aspect it would appear appropriate to group it with the B-complex.

Hæmoglobin and the Plasma Proteins

It is well known that hæmoglobin production in anæmia can be controlled by diet—more specifically that iron and protein stores or intakes are essential factors. Hahn & Whipple (1939) have clearly demonstrated that, by limiting

the protein intake in anæmia, hæmoglobin production can be reduced. When the erythrocyte and its contents disintegrate, much of the globin is saved and is probably used again to form new hæmoglobin or to supply some other protein needs of the body. Hæmoglobin production is modified by infection and to some extent in the later stages of nephritis (Whipple, 1942). Robscheit-Robbins, Madden, Rowe, Turner & Whipple (1940) have found that in dogs given abundant iron, but bled almost daily to maintain an anæmia level of about one-third normal, two to three times as much hæmoglobin was produced as plasma proteins even when the stimulus was apparently maximal.

The source, production and utilization of the proteins of the plasma were reviewed in 1940 by Madden & Whipple and again in 1942 by Whipple. The evidence is clear that the liver is of primary importance in the production of plasma proteins, although some globulin may be produced elsewhere: there is in fact evidence that fibrinogen is wholly dependent upon liver function.

Per unit of protein fed, beef serum will favour the production of three times as much plasma protein as beef heart, and more than five times as much as beef stomach: there is thus a qualitative as well as a quantitative aspect to the influence of food protein. Casein and lactalbumin have also been reported by some as having high potencies; low potencies are recorded for spleen, erythrocytes, brain, canned salmon, gelatin, pancreas, kidney and zein.

Animal protein is twice as effective as vegetable in combating œdema and hypoproteinæmia. For albumin production, it is unsafe to make sweeping assertions concerning the group-superiority of animal or of plant proteins. However, certain plant proteins, e.g. rice and potato, appear to favour a low albumin:globulin ratio, and are favourable for the production of globulins when compared with certain standard animal proteins. The body appears to use both albumin and globulin at about the same rate to carry on its normal internal protein metabolism. Under the condition of plasmapheresis there are indications that globulin formation is directly dependent on the diet. Cystine, under certain conditions, appears to act as a key amino-acid in plasma-protein regeneration. Methionine is not apparently an efficient substitute for it. Parenteral liver extract and iron are ineffective in regeneration in hypoproteinæmic dogs.

There is considerable evidence that a reserve of plasma-protein-building material exists in the organism and may be supposed to be part of the body stores. In the utilization of the reserve store for general N requirements or for plasma-protein formation, a large bulk of the store is used early and rapidly. The "labile" portion may be regarded as merely that portion of the reserve store which is mobilized first and fastest. The greater bulk of this reserve is not stored as plasma protein, nor as material more easily converted into plasma protein than orally ingested protein. The store yields albumin on depletion in slightly more abundance than globulin. The reserve store of protein may be regarded as all protein which may be given up by an organ or tissue under uniform conditions without interfering with organ- or body-function.

Sachar, Horvitz & Elman (1942) have shown in dogs that there is apparently a constant relationship or partition in the loss (or gain) between plasma-albumin and the total body-protein induced by diet, and that this relationship is of the order of 1 to about 30. Thus, for every g. of increase in serum albumin desired, about 30 g. must be retained for increases in other proteins of the body. These workers stress that this relationship applies only to alterations induced by dietary changes and cannot be expected to hold in cases of hypoproteinæmia due to blood loss, burns, nephrosis or liver disease.

Further, owing to dehydration and consequent blood concentration, the serum-albumin concentration may not reflect the hypoalbuminæmia of depleted patients. This is an important point which is frequently neglected. It was also found that when dogs rendered hypoalbuminæmic by a three weeks' fast were fed meat *ad libitum* the albumin appeared to reach a static level more rapidly than did the globulin.

Schoenheimer *et al.* (1942a), by the use of isotopic amino-acids fed to rats, have found that the plasma proteins share in the metabolic reactions involving the incorporation of dietary nitrogen, that the various fractions share to about an equal extent, and that the rate of the process is approxi-

mately the same as that found in the kidney, liver and intestinal tract of the same animal. Parallel investigations on the erythrocytes showed that both the protein and the porphyrin of the hæmoglobin had a lower "chemical activity" than the plasma proteins. It may be that the anæmia which is a frequent consequence of severe injuries is due, in part, to the lower competition-factor which hæmoglobin and/or the erythrocytes seem to possess in comparison with the plasma proteins.

The plasma-protein-forming mechanism is disturbed by the complicated body reaction to infection. Prolonged hypoproteinæmia *per se* causes no damage to the protein-forming mechanism. A steady state of "ebb and flow" exists between the plasma protein and the cell- and tissue-protein. The ultimate source of the construction-materials is food protein, furnishing amino-acids which are synthesized in the liver cells (and elsewhere) into plasma proteins. This same influx of amino-acids and/or plasma proteins, supports protein formation throughout the body. A part of the body protein forms a reserve against adversity in the sense that it can be depleted without obvious injury to the body. It has been termed "the bulwark against infection".

Elman (1943), Wilensky (1944) and others have also reviewed the subject, more especially from the clinical viewpoint. Deficiency of plasma protein (hypoproteinæmia), including lessening of the normal reserve, occurs in conditions of deficient food intake (hunger-œdema), or of digestive capacity or absorption. It is frequent in bleeding peptic ulcer, carcinoma of the alimentary canal, intestinal obstruction and in patients with intestinal fistulæ. It is also found in liver diseases, and in forms of traumatic, toxic or chemical injury to the liver. In severe thyrotoxic disease, there is, in addition to the increased catabolism of protein, an associated parenchymal lesion of the liver. Hypoproteinæmia occurs also in renal conditions where albuminuria is an important factor. In certain severe conditions accompanied by excessive loss of nitrogen due to abnormal destruction of tissue, there are large losses of nitrogen in the urine, and the tissue and reserve stores of protein become abnormally depleted.

The general pathological changes due to hypoproteinæmia are those resulting from the disturbance in water distribution, namely, œdema of the subcutaneous tissues and of various viscera. Lesions of the tissues other than those associated with œdema commonly take the form of defects in protein tissue—partial disappearance of the cardiac muscle fibres and of skeletal muscle, fatty metamorphosis of the hepatic lobules with areas of necrosis in the mid-zonal areas, loss of substance and increased water content of the hepatic cell. The deleterious effect of hypoproteinæmia in the healing of wounds appears to be limited to the proliferation of the fibroblasts, but may well have more widespread effects.

Protein deficiency with anæmia occurs after severe injuries—particularly after extensive burns—following the actual loss of tissue, and of plasma in the exudate.

Reversal of the albumin:globulin ratio, which is normally 1.6 to 1, is found in advanced hepatic damage. Even where there is no reversal in such cases, the alpha, beta and gamma globulins are in abnormal distribution, the gamma form being present in increased proportion. In the hepatic type of hypoproteinæmia, the severe damage of the liver renders the low level of plasma protein relatively unresponsive to treatment, and the result depends largely on the length of time the hypoproteinæmia has been present, and on the amount of irreversible damage that has preceded the treatment. In most other forms of hypoproteinæmia, replacement therapy is usually effective, provided that the cause is removed. Replacement therapy may take the form of protein or amino-acids by mouth; transfusion of blood, plasma or serum; the reinfusion of ascitic fluid; and the parenteral administration of amino-acids alone or with blood, plasma or serum.

Kagan (1943) has pointed out that hyperglobulinæmia is chiefly found in diseases of the bone-marrow, chronic infection, diseases involving the liver, and dehydration. Hyperalbuminæmia rarely, if ever, occurs.

Feeding with Protein Hydrolysates and Mixtures of Pure Amino-Acids

When it was realized that extensive hydrolysis of protein was an essential preparation for the absorptive processes, and that amino-acids were absorbed from the intestine during digestion in amounts sufficient to account for all the nitrogen

digested, it was but a step to consider the administration of the split products themselves. Henriques & Andersen in 1913 demonstrated that nitrogen equilibrium could be maintained in the goat with intravenously injected amino-acids as the sole intake of nitrogen. The therapeutic implications of this did not follow until 26 years later, although the possibility of supplying amino-acids parenterally had been suggested from time to time, particularly by Rose (1934-35). In 1939, Elman & Weiner reported the application of a protein hydrolysate to the intravenous alimentation of human subjects. The preparation used was an acid hydrolysate of casein fortified with tryptophane (which is destroyed during digestion with acids), and supplemented with additional methionine or cystine, as they considered that the level of the sulphur-containing amino-acids in casein was not optimal for their purpose. Evidence of utilization, experimentally and clinically, as well as therapeutic effects in patients were observed by Elman & Weiner.

Cox & Mueller (1939) next reported that an enzymic hydrolysate of casein containing all the amino-acids of casein was capable of maintaining nitrogen balance and promoting growth. Clinical observations on this product by Shohl, Butler, Blackfan & McLachlan (1939) and by Farr & MacFadyen (1939, 1940) followed. The indications were that it was well utilized, but that reactions might be observed. With improved methods of preparation, the occurrence of reactions has almost completely disappeared, and thousands of intravenous infusions have now been given, particularly with enzymic hydrolysates of casein or meat. Casein digested by pork pancreas has largely been used in the United States by Elman and his co-workers and by many other workers there (literature reviewed by Martin & Thompson, 1943, and by Gaunt, 1944). Whole beef-serum has also been used (Melnick, 1943). A papain digest of casein, although it does not carry the digestion quite so far as trypsin, has been used experimentally by Madden, Zeldis, Hengerer, Miller, Rowe, Turner & Whipple (1942), and Beattie, Herbert, Wechtel & Steele (1944) have stated that they have used with success a hydrolysate of casein produced by submitting the protein first to the action of papain and then completing the digestion with trypsin. From India come interesting reports on the preparation and clinical use, in the Bengal famine, of papain digests of meat (Narayanan & Krishnan, 1944; Krishnan, Narayanan & Sankaran, 1944).

In order to prevent the amino-acids from being utilized mainly for energy purposes, it is always necessary to give carbohydrate simultaneously and, when they are given by vein, glucose is added to the hydrolysate. Hydrolysates are usually administered in 2.5%, 5% or 10% strength.

It is obvious that there is no point in giving protein hydrolysates to patients who can ingest, digest and absorb sufficient protein to serve their requirements. It is only when the capacity to ingest, digest or absorb is affected that their administration is indicated. Orally, if suitably flavoured, they are a compact form of giving considerable amounts of amino-acids, particularly in conditions where appetite is lacking and the need for amino-acids is acute. Intravenously, they are useful as a temporary measure in supplying amino-acids in conditions where oral feeding is impossible or inadequate. Elman (1940) has reported a patient who had injections of 80 g. hydrolysate per day over 13 days. Taylor, Levenson, Davidson, Browder & Lund (1943b) have reported a patient who, as a result of extensive burns, became so desperately ill that excessive forced alimentation had to be attempted. This patient, fed by both vein and stomach tube, received some 500 g. of protein daily, of which up to nearly 200 g. were given by vein. This enforced feeding was maintained for more than 42 days and the patient is stated to have made a remarkable recovery.

In the Bengal famine of 1943, 25% of the cases of inanition removed to hospital were almost moribund. They were unable to take even fluids by mouth. The immediate reaction to the glucose-hydrolysate mixture was usually good, and deaths due to inanition were reduced. In severe cases oral feeding was possible only after several injections. In some cases the improvement was not maintained and the patient died. At post-mortem examination, signs of serious complications were usually found; these were commonly indicative of dysentery, with extensive bowel ulcerations. The only contra-indication that Krishnan *et al.* (1944) have noted is nephritis. In such cases bad results have been seen. In liver conditions in which the deamination mechanism is

impaired, as indicated by raised amino-acid N levels, and perhaps low blood-urea, the administration of large amounts of amino-acids would theoretically be harmful. Where, however, there is sufficient hepatic function, and yet because of ascites the patient is unable to ingest an adequate amount of protein, parenterally administered amino-acids may be useful.

Difficulties in the preparation of pure amino-acids have prevented more than a very few human experiments with them. At least two such experiments have now been reported (Shohl & Blackfan, 1940; Bassett, Woods, Shull & Madden, 1944). In the latter case the 10 essential amino-acids, together with some glycine, were given in 50-g. doses morning and afternoon over a considerable period of time. The rates of injection tolerated were greater than any recorded for protein-digest solutions. No rise in body temperature took place; 10% glucose was also infused, and small oral feedings of carbohydrate and fat brought the daily caloric intake from all sources up to about 1,500 calories. Nitrogen equilibrium was achieved. It is of interest in view of the suggestion of Albanese & Irby (1943) that the *d*-forms of amino-acids might possibly be toxic, that the *d*- and *l*-forms of threonine, valine, leucine, isoleucine, phenylalanine and methionine were used without any evidence of toxicity.

The clinical indications for the use of protein hydrolysates and pure amino-acid mixtures have been discussed by Elman (1943), Elman & Lischer (1943), Martin & Thompson (1943) and Gaunt (1944). It is important to note that these hydrolysates or mixtures of amino-acids have not the colloidal properties of the blood proteins, and are in no real sense a blood-substitute, and that they should not be used routinely unless the ability to ingest, digest or absorb protein is seriously impaired. Further, it should be noted that, as at present arranged, only one or two proteins are administered in the hydrolysed form and their biological value will almost inevitably be less than that of the mixed proteins of a normal dietary. The indiscriminate use of these hydrolysates or artificial mixtures of amino-acids may lead to the discredit of a valuable therapeutic weapon.

Protein and Amino-Acids in Relation to Trauma and Wound-healing

The metabolic disturbance which results from injury can be divided into several phases. There is first the loss of tissue substance and the varying degrees of cellular damage at the site of injury. This represents an immediate loss of protein and the other cellular and intercellular substances. The anabolic activity of the living but partially-damaged cells in the neighbourhood of the lesion will be also disturbed. The amino-acid requirements to replace or heal the injured zone will naturally vary according to the nature of the tissue destroyed and the degree of fibrous repair. The more complex the tissue, the greater will be the proportion of fibrous tissue.

Depending on the severity of the wound and the loss of blood and/or plasma externally and into the tissue spaces, there will be a period of reduced blood volume and "oligæmic shock" may develop. There is thus a loss of protein from the circulating fluid which is probably only in part reversible. It would be out of place here to discuss the use of whole blood, plasma, serum, albumin, gelatin, isinglass, globin, etc., in the treatment of shock. It suffices to state that no substitute has yet been found which is as good as blood for the treatment of hæmorrhage, or plasma or serum to correct hæmoconcentration. Where damage to tissue exceeds in volume that represented by two closed or open hands, transfusion is usually indicated (Grant, 1944). Plasma and serum are frequently used in the treatment of hæmorrhage as they are more readily kept available, but when used in a volume exceeding two pints [about 1.14 l.] a careful watch should be kept on the hæmoglobin level or the erythrocyte count, so that whole blood may be given if anæmia develops (*Medical Research Council*, 1944).

It is only very recently that figures for the protein loss in the exudate of burns cases have become available and that their significance has been appreciated (Rossiter, 1943). Co Tui, Wright, Mulholland, Barcham & Breed (1944) have now found the loss of nitrogen in the exudate of a burned case to be at the rate of 0.42 mg./cm.²/24 hours, and in another case whose surface had been denuded by avulsion, the rate was as much as 2.26 mg. of nitrogen/cm.²/24 hours. These authors have calculated that for a 70 kg. man of 170 cm. in

height, a burn involving half the body surface would be equivalent to 23.75 g. of protein per 24 hours ($= 400 \text{ cm.}^3$ plasma or 114 g. lean meat) if the loss occurred at the rate found in the first case, whereas if it occurred at the same rate as in the second case, it would be equivalent to 124 g. protein per 24 hours ($= 2,000 \text{ cm.}^3$ plasma or 600 g. meat). The continued loss of plasma in the form of the exudate leads to oligæmia and this may cause "shock".

During the period of "shock" the blood-flow to the kidney, liver, etc. is cut down to preserve the circulation to the more vital centres, and the function of these organs suffers in consequence.

Following this period of shock, with its lowered metabolic activity and with return of urinary flow to normal, there sometimes appear in the urine the products of the damaged tissues. This is mainly found in severe injuries, particularly crushing injuries. [Bywaters (1944) has given an account of these changes in air-raid casualties.] There is later a rise in metabolic activity which has been termed "traumatic inflammation." This precedes actual repair and is characterized by hyperæmia, exudation, and leucocytic emigration. During this period, autolysis and heterolysis through tissue and leucocytic enzymes remove the tissue debris; and sloughs which are not absorbed may separate.

Observations, mainly on fractures, have been made by the author and his colleagues (Cuthbertson *et al.*, 1929-44b) over a period of years and have demonstrated that, with this rise in metabolic activity, there is a marked loss of nitrogen, sulphur, phosphorus and potassium. Parallel with the rise in nitrogen, there is a rise in temperature and in oxygen consumption; creatinuria is also a feature. Disuse-atrophy, although it produces an undoubted but small loss of nitrogen, sulphur and phosphorus, could not wholly account for these changes, as the loss of substance was not confined to the area of injury (Cuthbertson, 1929; Cuthbertson, McGirr & Robertson, 1939). This traumatic catabolism in man usually reached a maximum towards the end of the first week after injury and later slowly declined, though a negative nitrogen balance might persist for several weeks after injury. With severe injuries, the ingestion of a diet rich in protein or in calories or in both, did not maintain nitrogen equilibrium at the height of the catabolic period, though there was evidence that with such high diets the nitrogen loss was diminished. How far this led to an improvement in the healing process could not be determined (Cuthbertson, 1936). In rats it was found possible to reduce markedly this nitrogen loss following trauma, e.g. fracture, by injecting the animals with a crude alkaline extract of the anterior pituitary gland which was already known to possess nitrogen-retention properties. On the other hand, there was no evidence from this, nor from wound-healing experiments, that the extract of the anterior pituitary gland accelerated wound-healing (Cuthbertson, Shaw & Young, 1941a; 1941b). On the other hand, evidence was gained that the healing of skin-wounds in rats could be accelerated by giving dried thyroid gland (Barclay, Cuthbertson & Isaacs, 1944).

Interest in this aspect of injury has received considerable attention recently in America and confirmation of many of these findings are to be found in the Macy Foundation Reports of the Bone and Wound Healing Conferences during 1942-43. Albright & Browne have there postulated that the adrenal cortex produces an "N" or nitrogen- or protein-anabolic hormone and an "S" or sugar or anti-anabolic hormone. These hormones are normally balanced, but after trauma has occurred there is an initial phase lasting 24 to 48 hours in which there is an increased excretion of both "N" and "S" hormones, followed by a second phase lasting days, weeks or even months in which there is decreased excretion of "N" hormone and an increased excretion of "S" hormone. Eventually, if the organism survives, the two hormones come into balance, and finally there may be a compensatory phase where the "N" hormone production is increased at the expense of the "S" hormone. Testosterone appears to fulfil the role of the "N" hormone. In the light of previous experience the writer doubts that testosterone therapy will achieve more success than that achieved by simply inducing nitrogen retention with anterior pituitary gland extract.

The theory has been advanced that the period of increased metabolic activity which is the concomitant of moderate or severe injury, might well be one of increased protein

catabolism, involving the liberation of some essential key amino-acids for repair, and the oxidation of the others for energy purposes. In collaboration with H. N. Munro (Munro & Cuthbertson, 1943) the writer has found that when rats are injured (fracture) whilst subsisting on a protein-free diet, no disturbance of protein metabolism (traumatic catabolism), such as has been noted in normally fed controls, takes place, apart from a very slight rise in nitrogen excretion, probably due to the elimination of the products of muscle-trauma in the urine. This suggests that the protein catabolized is essentially derived from a labile reserve which could readily be exhausted. It has been shown (Cuthbertson *et al.*, 1937a, b, c) that with the ingestion of food in excess of that required to meet energy expenditure, there is built up a reserve of labile body-protein. Reference has already been made to Whipple's conception of a labile reserve (Whipple, 1938, 1942).

Somewhat the same changes were reported in experimental burns by Clark & Rossiter (1943), working in R. A. Peters' laboratory, but they are complicated in man by (a) the protein lost in the exudation from the "weeping" surface, especially of superficial burns, but present also during sloughing and the granulation period, (b) the effect of the coccal infections of the first week and the abundant mixed coccal and bacillary infections of the second to fourth weeks (deep burns) while the necrotic tissues are separating. The continued fever and chronic suppuration lead to a continued loss of tissue protein and to anæmia. Atrophy due to disuse and to reflex action is also considerable. Penicillin and other chemotherapeutic agents aid in suppressing losses due to infection. The extent of the loss of nitrogen has never been completely assessed, for data on the loss in the exudate have been lacking. The author calculates that, in the first ten days after a 60 % burn involving the whole thickness of skin, a patient may lose about 2 kg. of protein. The loss does not continue at this rate but gradually diminishes. Nevertheless the demands on the reparative process have to be met by a protein-depleted subject, and at a time when, by the very nature of the illness, appetite is reduced.

The recent observations by Lucido (1930), Browne (1942), Cope, Nathanson, Rourke & Wilson (1943), Taylor *et al.* (1943a, 1943b), Co Tui *et al.* (1944), Anderson & Semeneoff (1944) and others, have shown the extent of the protein loss in burns—a loss not fully appreciated until the recent figures of Co Tui *et al.* for the protein in the exudate became available. Previous estimations of the nitrogen balance are incomplete, and the apparent success in maintaining equilibrium as recorded by some observers may well be fallacious for the above reason. Co Tui and his colleagues have shown that, in the later stages, burned patients fed a diet high in calories and high in amino-acids, as administered in the form of a casein hydrolysate, could be kept in nitrogen balance. It is difficult to determine from the protocols how successfully a balance might have been achieved by giving more natural food. The administration of amino-acids in amounts equivalent to 66 g. nitrogen and calories to the extent of 6,550 is surely almost exceeding the physical capacity of the patient.

The plasma proteins, in particular the albumin, tend to fall and, if infection is present, the globulin may rise. Taylor *et al.* (1943a) have reported that of 81 burned patients studied, 40 had hypoproteinæmia, the degree of which appeared to be related to the severity of the burns.

In the later periods of the repair process and during convalescence there is a positive nitrogen retention, and the bodily losses are then made good. Restitution of the architecture of bodily function takes time.

Conclusion

In the foregoing paragraphs there have been sketched some of the main features of protein metabolism, which in itself is but one episode in cellular activity; not only is there change of material but there is change of energy. Although a little is known of the great activity of the organ proteins and of their continuous regeneration from the amino-acids of the fluids that bathe them, practically nothing is known of the regulation of this continuous chemical activity, which is so adjusted that there is normally no final quantitative or qualitative change in the composition of the tissues other than those appropriate to the stage of growth and sex of the organism. Here lies a practically limitless field of discovery.

In the past, pathology has been largely a study of morbid

anatomy and protein has been considered only in so far as it was the main material which took up dyes and so provided a picture of the histological structure. The pathologist is now tending to become a morbid physiologist and protein is no longer for him solely a clue to cellular configuration but is now an integral part of function, and his study con-

cerns the regulation of those chemical processes which lead to deformation and dysfunction. A somewhat similar transformation is taking place in the field of medicine and surgery. Evidence of this is particularly to be seen in the new approach to the study of diseases of the liver and the reaction to trauma.

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¹ [see BMB 518]

² [see BMB 99]

³ [see BMB 519]

487

AN EVALUATION OF THE VITAMIN-C POSITION

S. S. ZILVA, D.Sc.

Scientific Staff, Medical Research Council and Division of Nutrition, Lister Institute, London

Scurvy in human beings was one of the first diseases the aetiology of which was traced beyond any doubt to a faulty diet. It was also an interesting coincidence that vitamin C was the first among the organic accessory food factors to be isolated, identified and synthesized. Furthermore it was found that it could be synthesized with great ease and consequently at a lower cost than any of the other vitamins. This latter feature combined with certain chemical characteristics possessed by *L*-ascorbic acid has attracted a great number of uncritical workers, both in the clinic and in the laboratory, who were susceptible to the blandishments of a therapeutic novelty. It is not, therefore, surprising that the greater part of the literature on the subject is rather more plausible than convincing. Unfortunately, in spite of the strongly pressed advice of the cautious, this literature has had its influence in some fields where the authorities take charge of the public health. It will be seen from this paper that when the work done on the subject during the past ten years or so is brought into focus, an aspect is obtained which is quite different from that presented by the casual perusal of the voluminous and troublesome literature.

The Chemical "Methods"

One of the factors which contributed to the prevailing distortion of our knowledge of vitamin C was the application of the so-called chemical methods employed in its assessment. Pioneer biochemical researches have shown that antiscorbutic solutions were endowed with a strong reducing capacity which was more or less parallel with their antiscorbutic activity as assessed biologically on guinea-pigs. The most specific reagents in this respect were found to be dyes of the phenolindophenol class which became decolorized in the process of reduction. As was to be expected, vitamin C when isolated was found to reduce indophenol as well as other reagents. By using standardized solutions such as indophenol, iodine, etc., pure *L*-ascorbic acid can therefore be determined titrimetrically with the accuracy of a fraction of a milligram. This fact led to the development of multitudinous "methods" with "refinements," the purpose of which was not immediately evident to everyone. Unfortunately even indophenol is not specific for *L*-ascorbic acid and therefore, although a useful reagent in the hands of the cautious, its promiscuous use on extracts of animal and plant tissues led to the promulgation of faulty conclusions. Much misleading information was disseminated, especially when these "methods" were employed in the assessment of vitamin C in natural foodstuffs, particularly when cooked or processed. In heating products containing carbohydrates, certain antiscorbutically-inactive substances capable of reducing indophenol may be formed. When the heating is carried out in alkaline medium, reductone is produced from hexoses, whilst in acid solution reductic acid is formed from pectins and pentoses. The chemistry of the degradation process of the above precursors is complicated and at present obscure, but it was sufficiently known that it may seriously interfere with the assessment of vitamin C in such circumstances. For instance, while the indophenol reducing substance reductone may be formed in the process of heating in alkaline solutions, ascorbic acid is being simultaneously destroyed in the presence of air. The resulting

indophenol titration can thus be entirely misleading as an index of ascorbic acid. It is therefore not surprising to find that according to some workers no destruction of vitamin C takes place—a synthesis is even sometimes indicated—when vegetables and fruits are heated in the presence of alkali. Recent work has shown that the indophenol titration may to some extent be corrected for non-active substances. The procedure nevertheless still remains a dangerous weapon in the hands of the uncritical.

The Phenomenon of "Saturation"

There seems little doubt that the chief reason for the exaggerated views held by many on the requirements of vitamin C for maintenance of good health is the confusion of thought that prevails concerning the phenomenon of "saturation".

One definition of "saturation" in man is the condition attained when a more or less constant daily amount of the vitamin C is eliminated in the urine as a result of ingesting a constant daily quantity of the vitamin above a certain minimum. Under normal conditions, especially in towns, deliberate attention has to be paid to the constitution of the diet in order to maintain a condition of "saturation". "Saturation" is therefore in this sense abnormal. Many people apparently in the best of health are known to be "unsaturated" or even not to eliminate ascorbic acid in the urine for long periods, especially in the winter months. The degree of "unsaturation" in such cases may differ within certain limits, but there is every reason to believe that the condition in the most "unsaturated" of this category could be induced in "saturated" people by their existence on a totally scorbutic diet within a period which is extremely short in comparison with the time necessary to produce frank scurvy. Yet such expressions as "hypovitaminosis C," "vitamin C subnutrition" and even "latent potential scurvy" and "subacute scurvy" are being recklessly applied to this condition by many writers and thus unwarrantably confusing it with the condition of "unsaturation" prevailing at the latent border-line of scurvy. At present there is no definite evidence to show at what stage "unsaturation" may really begin to have an unfavourable influence on health, but what evidence there is suggests that it is likely to be in the zone immediately preceding the frank manifestation of the disease. The literature contains few cases of experimental scurvy in human beings, but recently two such cases have been reported* which have every appearance of being well-controlled experiments. In one case no subjective or objective signs of scurvy were observed in the subject after 100 days on a scorbutic diet. In the second case a feeling of fatigue developed only at the beginning of the third month. Measurements of this weakness by an ergograph, however, showed that "the number of contractions at the rate of one per second made by the right hand against a standard resistance showed only a slight drop during the period of vitamin C deficiency". Further "there was almost complete freedom from respiratory infection throughout the experimental period, covering

* [Crandon, J. H., Lund, C. C. & Dill, D. B. (1940) *New Engl. J. Med.* 223, 353; Rietschel, H. & Mensching, J. (1939) *Klin. Wschr.* 18, 273.]

the months of October to May. Only two very transient and mild attacks of coryza were noted, each lasting but a few days. In previous winters it has not been uncommon for the subject to suffer from frequent, severe upper respiratory infections." It is important to note that in the first case also the subject recovered easily from a cold which he developed after 45 days on the scorbutic diet.

The abuse of the "saturation" phenomenon is actually worse than is outlined above. A number of workers, in measuring what they call the level of vitamin C nutrition, use "test doses" for the purpose. The procedure consists of administering massive daily doses of several hundred milligrams of ascorbic acid, the size of the dose used varying with the individual worker, until the patient eliminates ascorbic acid in the urine. There again, the criterion for the end-point varies with the individual worker. It may be anything from the first appearance of ascorbic acid in the urine, to the excretion of 50 % of the "test dose"! It is evident that in most of these cases the result is not only saturation but also the loading of the blood stream with large quantities of ascorbic acid. In measuring the "level of vitamin C nutrition" these workers are therefore adopting arbitrary levels imposed by themselves in accordance with their degree of enthusiasm. These "levels" unfortunately have no obvious connection with the aetiology of scurvy. In addition they are using a criterion which is by no means standard. It may therefore be fairly questioned whether the "saturation" tests justify the interpretation placed upon them. There is even no evidence that the vitamin C in the tissues of "saturated" persons is stored for reserve purposes. Results obtained with guinea-pigs point to the contrary.

The Plasma Ascorbic Acid

The concentration of ascorbic acid in the blood is influenced by the quantity of vitamin C consumed, by the ascorbic acid content of the tissues, and by the function of the kidney to eliminate the vitamin. In "unsaturated" subjects it is carried to the tissue and disappears from the blood stream within a short time. When the dose is small, little, if any, is eliminated by the kidney under these conditions. When the dose is very high, particularly when it is introduced parenterally, some may be voided in the urine even before "saturation" is reached. When "saturation" is actually attained there is a tendency for the kidney to eliminate the vitamin which is circulating in the blood, and if no further ascorbic acid is supplied to the system extraneously, the tissue ascorbic acid will evidently pass eventually into the blood and be eliminated. During the phase of "saturation" the ascorbic acid concentration of the blood is controlled by several factors, such as the quantity of ascorbic acid ingested, the time which elapses after ingestion, etc. When "unsaturation" sets in, owing to the consumption of small quantities, or to total abstinence from ascorbic acid, the plasma content gradually sinks to very low values or zero. This need not necessarily indicate a vitamin-C deficiency, any more than the early stages of "unsaturation" as manifested by lack of urinary elimination of ascorbic acid. In the experimental case of scurvy mentioned above, the plasma ascorbic acid was determined daily and it was found that the content fell rapidly and reached the low value of 0.1 mg. per 100 ml. of plasma after about 9 days on the scorbutic diet. For about another 8 days the values vacillated at about that level and eventually the content uniformly declined to zero 41 days after the beginning of the experiment. It is doubtful whether ascorbic acid values of the order of 0.1 mg. per 100 ml. of plasma can be considered as significant. Even so, the experiment showed that the absence of ascorbic acid from the blood was attained after about 41 days on a scorbutic diet when normal health was enjoyed. It must be noted that in this subject the plasma ascorbic acid was zero for thirteen weeks before the first evidence of clinical scurvy became manifest. Therefore, like the "saturation" test, it cannot be accepted as a test for vitamin-C deficiency. Of course, in cases of latent scurvy which are indicated by a response to specific therapy, the zero value of the blood offers additional support to the diagnosis.

Vitamin-C Requirements

It is customary to measure the requirement of a dietetic constituent by the daily dose necessary to maintain good health. Such an assessment is fairly simple in the case of an animal. In the case of man, however, it offers, for obvious

reasons, great difficulties, and consequently the minimum dose has to be deduced by indirect means. During the last three decades or so, much detailed experimental work has been carried out on scurvy in the guinea-pig, and indications have been obtained that a quantitative relationship exists between the guinea-pig and man in several respects.* The minimum daily dose of vitamin C for man can therefore be deduced with a fair degree of probability in the following way. A daily dose of about 2 mg. of ascorbic acid not only prevents the production of macroscopic and microscopic lesions of scurvy in guinea-pigs on a scorbutic diet, but apparently also enables the growing animal to lead a normal existence. About ten times this dose is required to attain the maximum concentration of the vitamin in the tissues, i.e. to attain "saturation." The dose necessary to maintain "saturation" in man as measured by the urinary output of ascorbic acid varies within certain limits with the individual and is of the order of 50 mg. per diem. If the ratio between the minimum "saturation" dose and the minimum protective dose is the same in man as in the guinea-pig, the minimum human requirements would be of the order of 5 mg. daily. Compared with the high targets now often recommended this figure may at first sight appear alarmingly low. When, however, the very low vitamin C content of the diets consumed by a great number of apparently healthy people for long periods in this country, particularly in the winter, is considered in relation to the very low incidence of scurvy, a minimum protective dose of 5 mg. does not appear to be surprisingly small. In view of these considerations the daily intake of 30 mg. recommended by the League of Nations Health Organisation Technical Commission on Nutrition seems to be a reasonable target, as it is in all probability several times higher than the minimum protective dose and would not require the consumption of excessive bulks of vitamin-C-containing foods even in the winter. It must, however, be observed that the above intake is intended as a target value and consequently does not require strict adherence. There seem to be many indications that only when this daily intake falls to a value below 15 mg., or perhaps even 10 mg.—in other words when approaching the minimum requirement—that precautions are required.

As scurvy is a disease which develops because of the absence of a dietetic factor, it follows that the introduction of the daily minimum dose of vitamin C into the food should be sufficient to cure the disease eventually. This is supported by the fact that improvements in patients suffering from scurvy have been observed on ordinary hospital diets poor in the vitamin even before treatment was commenced. In order to effect a rapid cure, however, large quantities of vitamin C may have to be administered at first. In deciding on the size of the dose the condition of the patient must evidently be taken into consideration, and therefore the form of administration and the quantity to be administered must be left to the discretion of the physician. Doses of several hundred milligrams of ascorbic acid have been successfully used in the early part of the treatment.

Vitamin C and Diseases other than Scurvy

The isolation and synthesis of *L*-ascorbic acid was followed by an indiscriminate search for the possible use of the compound in a number of diseases. In some diseases, like hæmorrhagic states different in their pathology from scurvy, and in Addison's disease, in which the response could have been expected to be of a definite nature, it was found to be ineffective. Claims concerning the merits of the new compound were made by some workers in respect of other applications, e.g. dental disease, skin conditions, cataract, gastro-intestinal disturbances, immunity and resistance to infection, wound healing and surgical conditions, pneumonia, tuberculosis and diphtheria. At the same time, however, these claims were contradicted by the evidence produced by other workers which militated against the suggestion that *L*-ascorbic acid was beneficial in the treatment of these diseases. Furthermore, when positive results were obtained, the position was often obscured by the failure of the workers to appreciate two cardinal facts. In the first place, in some cases such as wound healing, the improvement could often be traced to the rectification of a genuine pre-scorbutic

* [The author has discussed this relationship in more detail in the following papers: Kellie, A. E. & Zilva, S. S. (1939) *Biochem. J.* 33, 153; Zilva, S. S. (1941) *Biochem. J.* 35, 1240.]

condition. In other cases such as gastric and duodenal ulcers, the effect was confused with the cause. The undoubted presence in some instances of a genuine vitamin-C deficiency was evidently brought about by the insufficiency of the vitamin in the diet used in the treatment, and consequently the deficiency was not connected with the aetiology of the disease. In general it may be said that so far no convincing evidence has been produced that vitamin C has an influence on any condition other than scurvy.

Conclusions

A careful examination of the recent literature on vitamin C does not then appear to give quite the same impression as that obtained by the casual perusal of numerous contributions on the subject, which are more often than not characterized by a certain missionary spirit, and which are not always sustained by objective reasoning. The common misconception of the phenomenon of "saturation", with the consequent formulation of the high requirements of vitamin C for the maintenance of good health, has been followed by many spurious activities. It has encouraged a great deal of unnecessary experimental work in order to preserve the vitamin C in stored, cooked, processed and dried foods, etc.—by no means an easy problem—which, considering the abundance of vitamin C in the vegetable and fruit products of most countries, served no real purpose. The unjustifiable stress

placed by the teaching of public bodies on the importance of ensuring high intakes of vitamin C must no doubt have been responsible for causing unnecessary strain on the public in general and on the housewife in particular, especially as the information disseminated was not always scientifically correct. It is indeed questionable whether the scientific knowledge on vitamin C obtained in the interval between the two wars has really added anything to our knowledge which has a bearing on practical nutrition. The crude assessments of the vitamin-C content of foodstuffs were in the early days in many ways more reliable than the supposedly accurate modern chemical "methods," as they were all carried out by the only dependable test, namely the biological test. If the accuracy of this assessment is not high, it is, at all events, sufficiently accurate for the classification of antiscorbutic foods such as is needed for practical purposes. It is true that synthetic *l*-ascorbic acid has its advantages in certain cases of human disease, but this is by no means balanced by the gross and unwarranted abuse of the compound for general nutritional purposes. No doubt this biochemically interesting compound calls for much research, and may even reveal some unexpected therapeutic merit other than as a specific for scurvy, in medical practice, but useful results in this field can be obtained only by laboratory workers and clinicians who can impose upon themselves the strictest rules of observation and control.

OBSERVATIONS ON WATER METABOLISM

R. A. McCANCE, M.D., F.R.C.P. & W. F. YOUNG, M.D., B.Chir., D.C.H.

Department of Medicine, University of Cambridge

All the chemical reactions, which together constitute life, as we know it, take place in water or at a water interface. Life without water, therefore, is an impossibility, and it is a well known fact that the body of an adult contains some 72 % of water. It is not so generally known that the body at birth contains considerably more, but this is well established, and a fall in the percentage of water is one of the chemical characteristics of growth.

Effect of Reduced Intake

Man is surprisingly sensitive to a reduction in his water intake. Anyone can demonstrate this to himself and his friends by a very simple and perfectly safe experiment. • All he (or she) has to do is abstain from all liquid for three or four days, and to eat only "dry" food such as biscuits, cheese, jam, sugar and chocolate. By the third day the experimenter will probably have lost from 8 to 16 pounds [about 3.5 to 7 kg.] of weight. He will be very thirsty, but not perhaps inordinately so, and he may even maintain that he feels quite well, though he can no longer eat the dry food, and finds it a little difficult to talk for long at a time. His friends, however, will have observed a gradual change in his appearance. His cheeks will have become paler than they ought to be, and somewhat sunken; his lips will look dry, and they will probably have developed a slightly bluish tint. If the subject of this experiment decides to bring it to an end, and drinks two or three cups of tea, his friends will probably notice the most dramatic change in his appearance, and within 10 minutes he will have recovered all his characteristic colouring and be looking the picture of health once more. It may, however, take him some hours of steady drinking to regain his loss of weight (Nadal, Pedersen & Maddock, 1941; Black, McCance & Young, 1944).

Sources of Water

Man gets the water for his daily needs from three main sources. The first and most obvious of these is the water, coffee, tea, beer, soup or other liquid which he drinks. The second is the water in the so-called solid food. This may be a considerable amount, for some foods which look very solid contain a surprising quantity of water. Cabbages and marrows, for instance, may contain 95 % of water, and apples as much as 90 %. Meat again is more, and bread not much less, than half water. The third source is the water formed during the combustion of the food materials, for all of them are normally burned to CO_2 and water. A gram of

protein or sugar burns to about 0.5 cm.³ of water and a gram of fat to 1 cm.³, so that the metabolism of 100 g. protein, 100 g. of fat and 400 g. of carbohydrate will give rise to about 300 cm.³ of water. This is not enough for a man's daily needs, but some insects such as clothes moths must be able to live on the water which they derive from the oxidation of their dry, if somewhat valuable, rations.

Water and Salt Balance

If, as already implied, man is to remain efficient, he must be maintained in water balance, and he must, therefore, be supplied with enough water to replace the large amounts which he loses every day through the lungs, kidneys, and skin (Peters, 1935). The air expired by the lungs must always be saturated with water vapour, and the daily loss through this channel comes to about 400 cm.³ in a person taking a minimum amount of exercise, and in a temperate climate the losses by the skin can be cut down to a figure not much greater (Futcher, Consolazio & Pace, 1944). If 1,000 cm.³ per day be taken as the amount of water required in temperate weather by the skin and lungs, no great error will have been made, but in a hot climate a man may lose 14,000 cm.³ by the skin in the course of a day (Hunt, 1912) and all this loss is essential if the man is to survive, for were he to stop sweating his temperature would rapidly rise to a level that was incompatible with life.

Now sweat is essentially a dilute solution of sodium chloride, but since it contains very much less of this salt than the plasma, sweating will always lead to a concentration of the body fluids. If, however, sweating is very profuse and continuous, considerable amounts of salt may be lost as well as water. If the subject now drinks water freely, he may so dilute his body fluids that he is seized with the most severe cramps and becomes seriously ill. This can be prevented by the simple expedient of adding a small quantity of salt to the drinking water of men who are working in a very hot atmosphere. It is wiser to do this than to rely on a larger intake of salt at meal times, for men may eat less food for many reasons and still continue working and drinking. Such men are very liable to suffer manifestations of salt deficiency. Salt, however, should not be added to the water unless the heat is very great and the subjects have free access to water while they are at work. It would be a great mistake to add salt to the drinking water if the supplies were limited.

Man loses a good deal more water through the skin than certain other animals. This gives him an advantage over

the dog, for instance, in a very hot desert climate, for he can do hard work and still keep cool by sweating. The dog does not sweat, and normally cools himself by panting and protrusion of his moist tongue, but in the heat of the desert sun the animal rapidly becomes a casualty because his skin becomes unbearably hot and his temperature steadily rises. In a more temperate climate, however, the dog would have the advantage over the man if both were deprived of food and water, for the man would soon get very thirsty, while the dog could live quite comfortably on the water in his own tissues, which were being broken down, and on his own water of metabolism.

The human kidney is forced to pass out about 500 cm.³ of water a day with the urea and other solids which it excretes. The actual amount of this obligatory excretion depends upon the amount of solids, and particularly the amount of salt, which the urine contains. If the diet has contained little salt, or if sweating has been profuse in a hot climate, the urinary chlorides may be low and the obligatory volume not much more than 300 cm.³. It can be raised experimentally by taking salt (McCance & Young, 1944). The rest of the water passed by the kidney may be regarded as the surplus of intake over the essential requirements. This surplus amounts only to some 200 to 2000 cm.³ per day whatever the work or climate, which shows how well the intake is normally regulated by the desire to drink (Smith, 1937). This mechanism, however, is not perfect, for it is clear from the way in which people lose weight at the onset of really hot weather, and from the very small volume of urine passed during such weather, that the sensation of thirst may not be strong enough to prevent men getting into a state of hydropænia. It is, therefore, very important that administrators, medical men and others responsible for the welfare and efficiency of troops working in high temperatures should ensure that the men in their charge have free access to cool water day and night, and that they are encouraged to drink it. It is equally important to see that such working men are provided with enough salt to replace the amounts lost in the sweat.

Within the last few years the exigencies of war have forced men and women to live for many days and even weeks in open boats, and the question of drinking sea water has come up again and again. Now sea water may be regarded as a 3% solution of common salt, and the fluids bathing the cells of the body as a 1% solution. The kidney can excrete a 1% solution of salt, but no more, so that taking sea water by mouth can only lead to a concentration of the body fluids, which is the one thing that shipwrecked mariners are trying to avoid. But for the timely aids of science, which are now being made available (Spealman, 1944), Coleridge's lines are as true to-day as they were when they were written:

Water, water, everywhere,
Ne any drop to drink.

Marine Animals

How, then some may ask, do the marine mammals manage to survive, and how do the sea fish manage their water economy? The body fluids of these animals are no more concentrated than a man's, in spite of their hypertonic surroundings. The seals and whales need less water than man for they have no losses through the skin. They do not drink the water in which they live, in fact, they are careful not to do so, and only swallow their food after separating it from the sea water. They live on the water which their prey contains, and the water derived from its metabolism. The bony fish do drink sea water, but they have cells in their gills which excrete salt outwards, and so, although their kidneys are much less effective than those of mammals at excreting salt, they manage to maintain their body fluids at an osmotic pressure near to a 1% solution of

sodium chloride. The elasmobranch fish have a different mechanism. Their body fluids contain 2% or more of urea. Their gills are impermeable both to urea and salt, and they have so much urea inside them that their body fluids have a higher osmotic pressure than the surrounding sea. Consequently water passes into the animals and provides their kidneys with the means of excreting the waste products of the body (McCance, 1936; Krogh, 1939).

Water and Salt in Illness

Unlike other animals, man can exist for a long time outside his natural habitat, but only if by his forethought he has provided himself with the things which are essential for life. Of these water is second only to oxygen, and it should always be given precedence over food in lifeboats and rafts when space is limited.

When a man is ill, his requirements for water are almost as great as they are when he is up and about, and they may be much greater, for some diseases are characterized by a forced excretion of water. If this excretion is taking place by the bowel, it will be accompanied by a loss of salt, and both will have to be replaced. The usual way of doing this is by giving isotonic saline intravenously, and this is often a life-saving measure, but the use of saline can be overdone—particularly in young children. The mistake is made by those who cannot distinguish between water requirements and salt requirements. Although the metabolism of salt is intimately associated with the metabolism of water, the requirements of the two should not be confused. Saline should be administered only if there has been a loss of body fluids, and preferably when this loss has taken place to the exterior by vomiting or diarrhoea. Internal "loss," as in shock, is a separate question, and it should be treated usually by the administration of human plasma. Patients in need of water and unable to take fluids by mouth, as may often be the case after surgical operations, should be given a 5% solution of glucose intravenously. This provides them with a certain amount of food, and water to make good their losses by the lungs and skin. The simplest way of making sure that a patient is being given enough water is to test the specific gravity of the urine (Lashmet & Newburgh, 1932; Collier & Maddock, 1935; Jones & Morgan, 1938; Arnott & Young, 1942).

The dangers of giving moderate amounts of saline with the idea of treating dehydration may be illustrated by the following simple calculation. Let us suppose that a patient is unable to take anything by mouth, and that, in consequence, he is given, during 24 hours, 1500 cm.³ of normal saline intravenously, i.e. 1500 cm.³ of water and 15 g. of salt. He will require 1000 cm.³ of this water to make good the unavoidable losses from his lungs and skin, and so his kidneys will have the impossible task of excreting 15 g. of salt in 500 cm.³ of water. The kidneys may excrete most of the 15 g. of salt, but they can do so only by drawing upon water which was already in the body. Hence the administration of 1500 cm.³ of saline could only make the patient more dehydrated, while 1500 cm.³ of 5% glucose would have met all his water requirements. The casual administration of saline to very young infants is even more dangerous than it is in adult life, for the infant kidney is much less capable of dealing with the superfluity of salt (Young, Hallum & McCance, 1941; McCance & Young, 1941). It is, in consequence, very easy to raise the concentration of salt in an infant's body fluids to a level which must interfere with the child's well-being (Aldridge, 1941). It is a safe rule never to give 1% saline except specifically to replace a loss by vomiting or diarrhoea. All other fluid given should be salt-free or contain much less salt, and 5% glucose or 5% glucose in 0.2% saline are satisfactory solutions for the intravenous route.

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¹ [see BMB 507]
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MINERALS IN HUMAN NUTRITION

E. M. WIDDOWSON, B.Sc., Ph.D.

Department of Medicine, University of Cambridge

Students of nutrition have never produced discoveries of such immediate popular interest as the sulphonamides or penicillin, but it is probably true to say that by their united efforts they have done more for mankind than all other medical investigators put together. Nor are their labours completed. Every year some new advance is made and more and more opportunities of applying existing knowledge are discovered.

Interest in mineral nutrition has always tended to centre on those elements which are likely to be deficient in quantity or which may do harm by their excess. Every physiologist knows that magnesium is essential for life and that zinc has recently been discovered to be a component of the carbonic anhydrase enzyme system, but nutritionally these two elements are uninteresting, for no one has ever produced evidence to show that either of them is likely to be deficient in human diets, or present in a dangerous excess.

Our knowledge of the laws which govern the absorption and excretion of minerals has expanded considerably during recent years, and some general principles have now become firmly established. One is that minerals are much more readily absorbed if they are in solution, and consequently any ion which precipitates another in the stomach or intestine will, *ipso facto*, prevent its absorption. Soluble aluminium salts, for example, will inevitably react with phosphates and precipitate them irreversibly in the gut (Street, 1942; Kirsner, 1943). This is the mechanism which enables phytic acid to impede the absorption of calcium, magnesium and iron, and probably other divalent metals such as zinc and lead (McCance & Widdowson, 1942; Wang, Liu, Chu, Yu, Chas & Hsu, 1942; Krebs & Mellanby, 1943). Oxalates prevent the absorption of calcium (Bonner, Hummel, Bates, Horton, Hunscher & Macy, 1938), and calcium of oxalic acid (Barrett, 1942), and those who fear the formation of oxalate calculi in their urinary tracts should therefore take plenty of milk with their rhubarb. The converse of this also appears to be true, and agents which improve the solubility of an element in the intestine also improve its absorption. It is for this reason that proteins improve the absorption of calcium and magnesium (McCance, Widdowson & Lehmann, 1942), for their constituent amino-acids form soluble coördination compounds with the carbonates and phosphates of these two metals. This all sounds so obvious when it is enunciated that it is essential to think oneself back into the state of knowledge existing only a few years ago to appreciate the work undertaken to establish it.

Calcium

The insolubility of the carbonate and phosphate of calcium at the pH of living tissues is the clue to much of the physiology of this element, for it explains its usefulness as a hardening agent in bones, teeth and shells, and also its poor absorption and tendency to precipitate in unwanted situations. The absorption of calcium from foods of different kinds has occupied a good deal of attention in recent years. This is very appropriate, for few foods except milk and cheese contain much of this mineral and there is not enough milk at present to supply the world with its calcium requirements. In times of calcium shortage the amount of calcium in the drinking water assumes greater importance, and it has been calculated (Widdowson & McCance, 1943) that up to 200 mg. of calcium per day may be obtained from drinking water in districts where the water is hard. This is as much as there was in the adult milk ration in Britain during the winter months of 1942 and 1943. The same authors have shown that the cooking of vegetables in hard water makes a small, but only a small, difference to the total calcium intake. Basu, Basak & De (1942), Basu, De & Basak (1942) and Basu & Ghosh (1943) have concluded that the calcium in the bones of small fish and in lime chewed with betel* nuts is partially absorbed, and Breiter, Mills, Rutherford, Armstrong & Outhouse (1942) have shown that the calcium in carrots is about half as well utilized as the calcium in milk.

There is no doubt that the calcium intakes of at least half

the population of the world are much too low, and it is an unfortunate combination of circumstances that in these countries where the supply of milk is grossly deficient the diets very often consist mainly of whole cereals. As long ago as 1925 Mellanby discovered that there was some connection between the severity of the rickets developed by a growing dog and the type of cereal upon which it had been fed. Oatmeal was highly rachitogenic, whereas white wheat flour was relatively innocuous. At the time, and subsequently, the general importance of this discovery was missed, mainly perhaps because the experiments centred upon the production of rickets in growing animals and its cure by vitamin D. The last was therefore regarded as the important variable. In 1939, Harrison & Mellanby demonstrated that phytic acid played a large part in the rachitogenic action of cereals.

Until very recently it would have been safe to say that in spite of a great deal of highly suggestive work, vitamin D has remained the centre of interest in calcium metabolism, and the nutritional properties of cereals have been regarded as beyond practical control. The necessity for making the available wheat feed as many mouths as possible has revived interest in this problem, and McCance & Widdowson (1942), by means of prolonged metabolic studies with humans, showed that both calcium and magnesium were absorbed less freely from diets containing large amounts of brown flour than they were from similar diets containing white flour. Flour of 85 % extraction has also been shown to have a mild inhibitory action upon the absorption of calcium (Krebs & Mellanby, 1943). By adding sodium phytate to white flour, and by removing phytic acid enzymatically from brown flour, it has been shown (McCance & Widdowson, 1942) that the deleterious effect of brown bread on the absorption of calcium and magnesium in man is entirely due to phytic acid. The insolubility of the calcium salt of this complex acid radicle enables it to immobilize calcium from the rest of the diet in the intestine and so prevent its absorption.

Whatever the daily allowance of calcium ought to be, and it must, of course, differ from one individual to another, it is certain that many children in India (Wilson & Widdowson, 1942), Ceylon (Nicholls & Nimalasuriya, 1939), and Spain (Robinson, Janney & Grande Covián, 1942) have been existing on deplorably low intakes. Anything that can be done to raise the calcium intakes of poor people generally will undoubtedly benefit them, but the practical difficulties may be very great, particularly in a self-supporting, non-industrialized country such as India.

In Great Britain, flour was fortified with calcium in 1942, shortly after the extraction had been raised to 85 %. This measure was introduced partly to counteract the effect of the phytic acid in the 85 % flour, and partly to increase the calcium intake of a population whose milk supplies were reduced. Its wisdom has been demonstrated by the experiences of other countries which have not introduced such legislation. In South Africa, for example, where there has been a great increase in the consumption of high-extraction flours, measurable decalcification of the bones of the general population appears to have taken place (Meyer, Oosthuizen & Shapiro, 1942). Eire, however, has staged an even more significant large-scale experiment. Early in the war the shipping position forced the government of Eire to mill all the wheat available for human consumption to 100 %. The Dublin poor subsist largely on bread, and have very little milk, and this measure involved an enormous increase in their ingestion of phytic acid. No steps were taken to increase the amount of calcium in their diets, and in recent years there has been a serious increase in the incidence of rickets in the capital (Pringle, Reynolds & Jessop, 1943).

Striking evidence of the widespread improvement in mineral nutrition which has taken place in London during the last 25 years has been provided from comparative studies of the teeth of two large series of London schoolchildren by Mellanby & Coumoulos (1944). Teeth are laid down and formed long before they erupt, and it is necessary to seek the reasons for this improvement in earlier years. An increased intake of calcium has certainly played a part, but it is likely that vitamin D given to the children themselves, and to their mothers at the ante-natal clinics before they were born, has

* [The betel nut is the seed of the *Areca* palm (*Areca catechu*). It is usually chewed with lime and the leaf of *Piper* *Betle*, sometimes with the addition of other ingredients. The habit of betel chewing is extraordinarily widespread. It has been estimated that 200,000,000 of the human race are addicts.]

also helped to bring about the change. It is well known that vitamin D administered to women during lactation passes into the milk, but it has now been shown that administering calcium to mothers does not raise the concentration of this element in their milk unless vitamin D is given concurrently (Ritchie, 1942). It must not be overlooked, moreover, that there has been an improvement in the general nutrition of London children, and this may have been the most important factor of all in improving their teeth, for calcium metabolism is certainly connected with vitamin A and vitamin C, and the formation of bones and teeth must depend upon many other factors of which nothing is yet known.

Iron

It is well known to all analytical chemists that great precautions have to be taken to avoid contamination when iron analyses are being made, and metabolic experiments involving iron are difficult to carry out for this reason. Tables showing the amount of iron in foodstuffs are based on analyses of foods prepared with the greatest care to prevent contamination with extraneous metal. In the kitchen, however, no such precautions are taken. The housewife has her favourite kitchen knife, she has her mincer, and her chipped enamel pots and pans, and iron intakes as calculated from food tables should be regarded as minimum values. That actual intakes must sometimes be a great deal higher because of contamination from various cooking utensils was made clear from some experiments (Widdowson & McCance, 1943) in which it was shown that apples cut up with an ordinary kitchen knife and stewed in a chipped enamel pan contained 20 times as much iron as another sample of the same apples cut up with a stainless steel knife and cooked in a glass beaker.

Evidence has continued to accumulate during the past few years that the human body has no physiological method of regulating the excretion of iron, and that, in fact, very little is ever excreted. Thus, a patient with a severe hæmolytic anaemia, who was being kept alive by large and repeated transfusions, was found to be excreting none of the iron from her hæmolysed erythrocytes (McCance & Widdowson, 1943). The amount in the body must, therefore, be regulated by the amount absorbed, and Hahn, Bale, Ross, Balfour & Whipple, (1943) have published an account of an interesting though still very incomplete attempt to solve this problem by means of radio-active iron. They have found that the amount of iron absorbed by dogs depends upon the degree to which the small intestine has been saturated by the metal. Saturation by iron is rapid, and a large dose given a few hours before may block the absorption of a second dose containing the radio-

element. The removal of blood does not at once desaturate the mucosa, but this follows gradually as the iron stores are depleted to make good the loss.

Fowler & Barer (1942) and Barer & Fowler (1943) obtained some rather unexpected results when they followed the rate of hæmoglobin regeneration in blood donors who were being treated with iron. They found, in confirmation of previous workers, that when blood was first withdrawn the administration of iron shortened the period required for complete regeneration, but they also found that this beneficial effect was not so obvious after the second removal of blood, and negligible after later withdrawals. The puzzling feature of those observations is that the donors who were treated must have been absorbing far more iron than the controls, and many times more iron than they can have required for the hæmoglobin synthesis. These stores of iron were full and their serum iron-content was high, and the results only serve to emphasize the incompleteness of our knowledge of iron metabolism. They should not, however, shake our faith in the use of iron salts as therapeutic agents or in the necessity for ensuring that infants, pregnant women, and indeed the whole population, receive enough of this element for their physiological needs.

Trace Elements

Zinc, copper and manganese are certainly necessary for human nutrition, but there is some doubt about cobalt. Sheep and cattle require this element, possibly in connection with the micro-flora which they harbour in their intestines. The main interest of lead continues to lie in its toxicity. The two trace elements which have been most in the nutritional limelight in recent years are iodine and fluorine. Most of the work on fluorine has centred round its capacity to induce mottled enamel, and, in optimum doses, to prevent caries without disfigurement (Irving, 1941; McClendon, Foster & Supplee, 1943; Deatherage, 1943). A considerable amount of goitre still appears to exist in rural England. Most of this is thought to be due to an iodine deficiency, and it has lately been recommended that table-salt should be iodized (*Medical Research Council*, 1944).

A curious fact about iodine metabolism has recently been investigated (Flexner, Bruger & Member, 1942; Bruger & Member, 1943). It appears that iodides are selectively concentrated and excreted by the salivary glands of man. It is difficult to see any biological value in this, for the iodide will only be reabsorbed again lower down the alimentary canal. These glands will not excrete the iodine in *tetraiodophenolphthalein*, although of course, the liver selectively does so.

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NUTRITIONAL FACTORS IN DENTAL CARIES AND PARODONTAL DISEASE

J. D. KING, PH.D., D.P.D., L.D.S.

Nutrition Building, National Institute for Medical Research, London

The universal recognition of the high incidence of dental caries and parodontal disease makes it unnecessary to cite the exact figures disclosed by the innumerable clinical surveys

made in many parts of the world. It is sufficient here to state that diseases of the teeth or of their supporting structures (gum and alveolar bone) in general affect more than 90 % of

mankind at some period of their lives. The fact that these mouth lesions seldom lead to direct fatality perhaps accounts, in some measure, for the relatively slow accumulation of knowledge required to cope with this grave public health problem. Their detrimental influence on general health is, however, gradually becoming more widely appreciated, and this awakening is reflected in the demand for more and more investigations designed to discover the ways and means of eliminating oral disease.

Before the last world war, the "hygienic" conception of dental pathology predominated. Both dental caries and so-called pyorrhœa were associated with dirtiness of the mouth and other factors were dismissed as of little account. Caries was said to be the result of decalcification of the tooth enamel by the acid products of fermenting carbohydrate food debris retained about the teeth. Pyorrhœa and other forms of gum disease were claimed to be caused by the putrefaction of mainly protein elements of the food, resulting in breakdown of the gum-epithelium and the formation of pockets along the roots of the teeth, allowing subsequent infection and rarefaction of the subjacent alveolar bone. In order to prevent such conditions, decreased consumption of white bread, sugar, sweets, etc., and a proportionate increased use of so-called "detergent" foodstuffs were advised, with vigorous brushing of the teeth and gums as an additional precaution. Even to this day, dental health propaganda is largely based on these purely theoretical conceptions—and caries and pyorrhœa remain rampant.

In 1918 M. Mellanby published the first of a series of reports on the influence of nutritional factors on the development and structure of the dental tissues and their susceptibility to disease. Apart altogether from the intrinsic physiological and pathological significance of Mellanby's findings, a new era of dental research was begun. For the first time the experimental method was applied to problems of dental health, and elaborate theoretical essays based on empirical impressions were replaced by verifiable facts. It is possible to describe here only a few of the more important results of this changed conception of dental science, but in general it may be stated that the most outstanding involve the realization that the resistance of the dental and parodontal tissues to disease is closely related to those nutritional factors which govern the health of the body as a whole.

Dental Caries

Miller (1890) showed that test-tube mixtures of saliva with bread, sugar and other high-carbohydrate foodstuffs fermented on incubation at body temperature. If an extracted tooth were immersed in such mixtures it became decalcified by the acid products of the media and assumed an appearance somewhat similar to dental caries *in vivo*. An analogous enamel decalcification was postulated as the initial phase of caries in the mouth, and from this idea sprang the carbohydrate-fermentation hypothesis of caries. Recently, however, the original experimental basis for the theory has been more critically examined. For example, the *in vitro* lesions in Miller's form of artificial caries differ considerably from those of caries *in vivo*. In the mouth the most susceptible areas of the tooth are its pits and fissures, but in "test-tube" caries produced by carbohydrate fermentation the first regions to be affected are the tips of the cusps and biting edge of the tooth—regions where the natural disease never begins (King, 1937); indeed, the pits and fissures of the tooth remain singularly unaffected by the artificial lesions until a large area of the rest of the enamel is diffusely decalcified. Moreover, it has been shown (Pincus, 1937, 1939, 1944) that disintegration of enamel can be induced *in vitro* by the action of certain proteolytic micro-organisms recovered from the mouth and having their optimal activity in alkaline surroundings; and in this instance the initial breakdown of enamel does take place in those situations where the natural carious process is known to arise. Not only are the pits and fissures of the tooth crown highly susceptible to the disease but there is also a much higher proportion of organic material in these areas. "These facts may be of no little significance if eventually it be found that the initial phase of caries is in the form of a lysis of the protein elements of enamel rather than a decalcification of its inorganic constituents" (*Lancet*, 1944). The findings may indeed provide a reasonable explanation of the now known association between the susceptibility of a tooth to decay and the structure of the tissues comprising it, which

are in turn related to the calcifying properties of the diet. The clinical investigations of M. Mellanby and her colleagues (Dental Disease Committee, 1936; M. Mellanby, 1918, 1920, 1923, 1927, 1929, 1934; Mellanby & Pattison, 1926, 1928, 1932; Mellanby, Pattison & Proud, 1924) and others (Boyd & Drain, 1928; Boyd, Drain & Nelson, 1929; McBeath, 1932, 1934; Anderson, Williams, Halderson, Summerfeldt & Agnew, 1934; Schiotz, 1937; McBeath & Zucker, 1938; Boyd, 1940, 1943; King, 1940a; McBeath & Verlin, 1942) have shown clearly that nutritional factors such as vitamin D are of real significance in determining dental health, not only during the period of tooth development but even after calcification is complete. Further evidence in support of these contentions is supplied by an investigation in London reported during the present year (M. Mellanby & Coumoulos, 1944). On the other hand, no claim is made that increased consumption of foodstuffs rich in vitamin D, calcium and phosphorus will do more than reduce the ravages of caries, considerable as such a reduction might be.

Fluorine

Other factors undoubtedly play a part in the initiation and progress of the carious process and recent investigations have implicated the element fluorine. Numerous investigations have demonstrated that in communities whose drinking water contains about 1 part or more per million of fluorine, the incidence of dental caries is relatively low (Black, 1916; McKay, 1929; Ainsworth, 1933; Dean, 1938; Dean, Jay, Arnold, McClure & Elvove, 1939; Day, 1940; Sognnaes, 1940; Dean, Jay, Arnold & Elvove, 1941; Wilson, 1941; Murray & Wilson, 1942; Weaver, 1944). Indeed, the topical application of sodium fluoride to the teeth as a protective measure has already been reported (Bibby, 1942), while suggestions have also been put forward advising the reinforcement of the public water supply in areas where its original content of fluorine is below the 1 part per million level (McClure, 1943). That there are, however, still other factors to be discovered before full protection against caries can be accomplished is indicated by the findings of King (1944). A large field of research yet remains untilled before the human mouth can be rid of the dreaded fillings, forceps and artificial dentures.

Parodontal Disease

First it is well to mention that the term "parodontal disease" is here used to cover all departures from positive health of the tissues which surround and support the teeth, from very slight reddening and swelling of the gum margin to gingival atrophy, bone rarefaction and loosening of the teeth. Many aspects of the ætiology and pathology of the various forms of parodontal disease remain undiscovered. Both local and systemic agencies are involved but, while the nature of the former have long been recognized, identification of all the systemic factors is far from complete and their precise roles in the disease syndrome are still more obscure. Realization that food debris and tartar accumulating about the necks of the teeth lead to injury of the gum margin, and that these conditions are facilitated by irregular alignment or traumatic occlusion of the teeth, has led to the development of antiseptic and surgical measures designed to eliminate traumatic foci in the mouth (Stones, 1932a, 1932b, 1938). Such therapeutic procedures, aimed at establishing better mouth hygiene, have proved of real value in restricting the progress of established parodontal disease but unfortunately their effects are often only temporary. Moreover, while the severity of the lesions may undoubtedly be reduced, complete "normality" is seldom achieved. Indeed, without regular return visits to the dental surgeon for further observation and treatment, the original improvement may not be maintained. In other words, in the majority of cases there would appear to be some underlying systemic defect or defects which, if not determined and corrected, will retard if not prevent complete recovery of the affected tissues (King, 1943b). Foremost among these systemic disturbances must be placed deficient intake or utilization of various specific food factors, and account should be taken not only of acute vitamin deficiency but also of the possible influence of a sub-optimal supply of vitamins of relatively short or long duration.

Vitamin A

Since 1930 experimental investigations have demonstrated that vitamin A is essential for the proper development of the gingival epithelium (M. Mellanby, 1930; King, 1940b). Deficiency of this vitamin, especially during pre-natal and

early post-natal life, was observed to lead to epithelial hyperplasia and increased susceptibility to parodontal disease in later life. It was then found that, in the experimental animal, vitamin A deficiency also resulted in degeneration of the nerves to the jaws (M. Mellanby & King, 1934; King, Lewinsky & Stewart, 1938) and to excessive atypical alveolar bone, hypercementosis around the tooth roots, and retarded eruption with subsequent irregularity of the teeth (King, 1936; H. Mellanby, 1939). The end-result of all these changes was hypertrophy and later atrophy of the gingivæ, secondary invasion by micro-organisms, parodontal abscesses and loosening of the teeth—a series of events not unlike those associated with so-called pyorrhœa in man. The precise sequence of the changes in experimental A-deficiency is still not clear, but there is significant evidence that the nerve lesions in other parts of the body (and therefore presumably also in the mouth) are the result of compressive trauma from abnormal growth of the inner wall of the bony channels through which the nerves pass (E. Mellanby, 1938, 1941, 1943). The epithelial hyperplasia may be due to more or less direct stimulation of the epithelial cells, to loss of neurotrophic impulses from the degenerating nerve fibres supplying the tissue, to a combination of these effects, or to some as yet undetermined reaction to the lack of the vitamin in question. As regards the use of vitamin A in the prevention and treatment of human parodontal disease, little reliable information is available. On the basis of the animal investigations, however, we should be well advised to insist on a liberal supply of this food factor in the dietary of the expectant and lactating mother, and of her offspring at least up to puberty, in order to ensure that the gum epithelium and alveolar bone are properly formed. There would also seem to be an opening for vitamin A therapy as a supplementary measure before, during and after the surgical procedures employed in the treatment of established disease.

Nicotinic Acid

Since 1939 I have obtained some evidence* that the nicotinic acid component of the vitamin B₂ complex is of value in the treatment of ulcerative lesions of the gum (King, 1940c, 1943a; King & Francklyn, 1944). In this form of disease a fairly widespread superficial necrosis of many other parts of the buccal cavity may be seen, but the presence of one or more teeth appears to be an essential condition for its occurrence. The lesions bear no little resemblance to those seen in animals receiving diets deficient in the B₂ vitamins (Topping & Fraser, 1939). The precise ætiology of ulcerative gingivo-stomatitis (Vincent's disease) in man remains unsettled, but it is believed that the main pre-disposing agencies are local trauma of the gum, depressed general tissue resistance, often associated with and sometimes due to vitamin deficiency, and, coincident with or following these conditions, secondary non-specific bacterial action. During the past five years I have made detailed records of more than 800 cases of Vincent's disease and have personally treated some 500. In many instances administration of nicotinic acid or nicotinamide would seem to exert its beneficial influence by stimulating general tissue resistance, perhaps by restoring some broken link in the chain of tissue respiratory reactions, but supplementary local hygienic measures and sometimes tooth extraction are usually necessary to eliminate the traumatic foci and associated proliferation of anærobic micro-organisms. With regard to the possible infectivity of the ulcerative lesions much controversy exists, but my own opinion, supported by experimental self-induction of the characteristic disease (King, 1943), inclines to the view that the condition is likely to occur only in persons whose general resistance is depressed by defective nutrition or other illness, and whose mouths present more or less persistent traumatic foci.

Vitamin C

A large number of clinical investigations has been made of the effects of vitamin-C therapy on various forms of gingival

disease. Many authors believe that the antiscorbutic vitamin is of value in supplementing local hygienic measures (Kramer, 1937; Roff & Glazebrook, 1940; Campbell & Cook, 1941; Kent, 1943; Stuhl, 1943). On the other hand, cases of typical scurvy have been described in which no gum lesions could be found (Blackstone, 1942); a similar finding was reported in the experimentally induced human disease (Crandon, Lund & Dill, 1940). Disappointing results have also been recorded in the treatment of both ulcerative and non-ulcerative gingivitis with a fairly wide range of ascorbic-acid dosage (King, 1944). An interesting suggestion regarding the possible benefit of vitamin C in the treatment of diseases of the gums is that it may assist in the healing of injuries caused by local traumatism (Cook, Davidson, Keay & McIntosh, 1944), but the evidence for this is not conclusive.

Other Nutritional Factors

No mention has yet been made of nutritional factors such as vitamin D, calcium and phosphorus, which are intimately connected with the development of bone and other calcified tissues. Obviously, deficiency of these food essentials, by causing rickets, osteomalacia and allied conditions, will lead to the production of defective alveolar bone and crowding of the teeth, a state of affairs which would be further accentuated by the excessive consumption of cereals having a high phytic-acid content. On the whole, however, most forms of parodontal disease show their initial lesions in the gum and not the bone and, for this and other reasons, further discussion of this aspect of nutrition is unnecessary here. In addition to those already referred to above, there are, however, a number of other vitamins which may play some part in the maintenance of parodontal health, more particularly other components of the vitamin B₂ complex; but the published reports concerning them are conflicting. One important point of agreement appears to be that in many animals the sum of the known vitamin B₂ components in their synthetic state is by no means as effective as the whole complex in the form of less artificial products, such as yeast and liver preparations. This, incidentally, is also in agreement with the experience of clinicians in parts of India, Malaya, Africa and elsewhere, in the treatment of some types of stomatitis not usually encountered in more temperate climates.

Non-Nutritional Factors

Brief reference should now be made to systemic factors, other than nutritional, which may have a bearing on susceptibility of the parodontal tissues to disease. So-called "pregnancy gingivitis" has often featured in the literature and, while its frequent association with nutritional defects should not be ignored, there is a certain amount of clinical and experimental evidence that sex-hormones may here be implicated (Ziskin, Blackberg & Slanetz, 1936; Ziskin, 1937, 1939). Many workers have also commented on the undoubted accentuation of gingival disease in subjects affected by diabetes mellitus (Goldstein, 1938; Cohen & Rudy, 1942; Rudy & Cohen, 1942; Lovestadt & Austin, 1943), but this field is still largely unexplored. Another aspect of the problem worthy of further study concerns the experimental demonstration of an association between herpetic viruses and ulcerative lesions of the gum in children (Dodd, Boddington & Johnson, 1939; Scott & Steigman, 1941). Finally, the nature and mode of formation of tartar or oral calculus is of much importance since its deposition is related to gingival disease, at least in the lower incisor and upper molar regions of the mouth. In this respect many interesting observations have already been made (Bulleid, 1925; Adamson, 1929a, 1929b; Smith, 1930; Wilkinson, 1935; Glock, Murray & Pincus, 1938), and further work may again reveal a connection between local and systemic factors. Indeed, as with dental caries, study of the interplay of local mouth conditions with changes in the organism as a whole would seem to offer the most promising line of approach to the whole problem of oral disease.

* [see also *BMB* 104, 530]

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491

DETERMINATION OF VITAMINS BY PHYSICAL, CHEMICAL AND MICROBIOLOGICAL METHODS

J. R. P. O'BRIEN, M.A., B.Sc.

Department of Biochemistry, University of Oxford

Chemical, physical and microbiological estimations of vitamins are rapidly displacing the more tedious yet, as generally accredited, more reliable methods of biological assay. This is particularly true of that heterogeneous group of accessory food factors called the vitamin-B complex. The replacement of the time-consuming biological methods has originated from two developments in the vitamin field. First, the isolation and the characterization of the physical and chemical properties of vitamins paved the way for a number of colorimetric and physical methods. Then, the finding that many factors essential for animals are also necessary for some micro-organisms led to estimation of the factors by their growth-promoting effects on the latter. Often, in fact, the characterization of a microbial growth-factor has preceded the establishment of its need by man.

However, in their present forms none of the methods of vitamin estimation have attained that accuracy which is desirable. The chemical methods, which depend upon the presence within the molecule of a non-specific chemical group, are limited in their accuracy, and vagaries in the nutritional requirements of micro-organisms impose a similar limitation on microbiological methods. However, it can be said that, in general, these methods give values for the vitamin content of foodstuffs and tissues which are not far removed from those given by the biological methods. For some time to come, the more specific animal tests will continue to be necessary as a check upon the less specific chemical and microbiological tests, but in evaluating these it should not

be overlooked that there is a wide range of error inherent in animal tests. A blind faith in the infallibility of bio-assays may easily condemn methods which give the absolute, if not the physiologically available, vitamin content of a material.

War-time circumstances have had some part in the drive for the development of precise and rapid methods of vitamin determination. Experience of the last war has underlined the importance of vitamins in maintaining the nutritional status of the military and civilian population. Nor has the nutritional element been forgotten in the treatment of disease and of war casualties. In several ways analytical methods have helped to assure the vitamin intake of the individual. In checking the vitamin contents of natural and fortified foodstuffs, for estimation of the daily intake of vitamins, they have been used extensively. They have provided the means for numerous tests which, however inadequate they may be, seek to measure a person's nutritional status. No attempt will here be made to detail the methods in use or to exemplify the general applicability of any one method in the analysis of foodstuffs, tissues, blood and urine. For, often, the use of a method of proved value in the analysis of one foodstuff has not been fully explored in that of others.

General Considerations

It is particularly the water-soluble vitamins which have lent themselves to rapid estimation. Of these, aneurin and ascorbic acid, the first to be isolated, have received greatest attention; publications on the assay of vitamin C probably

exceed in number those on all the other vitamins. Of the fat-soluble factors, vitamin A can be estimated with certainty; for vitamin D there are promising methods and, for vitamins K and F, methods more in the developmental than finished stages are available.

Most of the vitamins are present in a combined form in tissues. Aneurin exists almost exclusively as a pyrophosphate in mammalian tissue (Ochoa & Peters, 1938). Nicotinamide is an integral part of the co-dehydrogenases, and riboflavin is a component of the flavoprotein enzymes. There is evidence for the combination of pyroxidin and pantothenic acid with protein. Vitamin A tends to exist in the esterified condition.

The existence of these combined forms necessitates, in most methods, liberation of the vitamin by chemical or enzymatic hydrolysis. In one or two instances the bound form can be estimated. For aneurin pyrophosphate Ochoa & Peters introduced a method, based upon the measurement of the CO_2 formed by the action of the pyrophosphate and carboxylase upon pyruvic acid, so delicate that amounts of 0.01 μg . could be determined. Estimations of this kind are important, as they determine the vitamin in a form in which it is biochemically active. Co-dehydrogenase 1 can be assessed by its growth-promoting effect upon *Hæmophilus influenzae*.

No method for vitamin assay has yet reached perfection. Each one seems to have its advantages and weaknesses. The chemical methods lack the specificity of the biological, although they yield highly reproducible results. Methods which measure the intensity of fluorescence of a vitamin or its derivatives must take into consideration the phenomena of quenching; changes of fluorescence with pH; substances acting as light-filters; and the peculiarities of the chosen apparatus. It is clear that, for precision, fluorimetry demands close attention to experimental conditions. Measurements of the absorption-spectra of vitamins yield accurate results when careful standardization of the instrument and experimental conditions have been made and relatively pure substances are used.

In microbiological determinations, the great care needed in deciding the growth-medium is emphasized by the frequent modifications which are introduced to improve the method. For example, the specificity of an organism may be reduced by its growth-response to derivatives of vitamins; or the growth of the organism may be influenced by unsuspected toxins in the test solution. To avoid these difficulties it would appear most satisfactory to concentrate upon the use of a few selected organisms. Among these should be included *Lactobacillus casei*. Introduced by Snell & Strong (1939) for the microbiological assay of riboflavin, this organism has been shown, as a result of replacing peptone and yeast-extract by pure substances, to need a large number of factors and amino-acids for its growth. In fact, it is claimed that *Lactobacillus casei* may be used for the analysis of six B-vitamins: pyridoxine, riboflavin, biotin, pantothenic acid, "folic acid," and nicotinic acid (Landy & Dicken, 1942).

B-Vitamins

Aneurin: The first colorimetric estimation of aneurin was that of Kinnersley & Peters (1927, 1934), who found that in moderately alkaline conditions the vitamin gave a pink colour with diazotized sulphanilic acid, which could be stabilized by formaldehyde. A modification of this test was developed by Prebluda & McCollum (1936, 1939), who used diazotized *p*-aminoacetophenone. With improvements, this method has been used for the estimation of the aneurin content of national flours and bread (Platt & Glock, 1943). A hydrochloric-acid extract of the flour is treated with superfiltrol; upon which the vitamin is adsorbed. The washed adsorbate is treated with the diazo reagent, and the resulting dye is extracted with toluene. For flours and bread this procedure gave values in good agreement with those obtained by biological and fluorimetric methods (*Medical Research Council*, 1943). It remains to be seen whether it is applicable to other materials.

A popular method for aneurin analysis originated from the observation of Peters (1935) that oxidation caused the production of blue fluorescent substances from the vitamin. The product of the oxidation, called thiochrome, was isolated and synthesized by Todd, Bergel, Fraenkel-Conrat & Jacob (1936). In 1936 Jansen adapted the oxidative formation of

thiochrome to the determination of aneurin. From that time his method has been subjected to numerous improvements and used widely in the analysis of foodstuffs and, in urine, in the so-called aneurin-saturation tests. Many materials must be treated initially with pepsin or takaphosphatase to free the aneurin from its combined forms. Purification of the extracts can be effected by adsorption of the vitamin upon *decalso*, a synthetic aluminium silicate, from which it is eluted by KCl solutions. Oxidation is achieved by alkaline ferricyanide and the thiochrome is extracted with *isobutanol*. The fluorescence-intensity of thiochrome can be estimated by matching visually against standards or by the Spekker fluorimeter. The method is not without its difficulties; one of which is the frequent occurrence of blue-fluorescent substance in tissues, another, the oxidative procedure. Its sensitivity is great. In the ingenious method of Hinton (1943), 0.05 μg . aneurin in cereal extracts can be determined with an error of $\pm 3\%$. The value of this method in those cases where only 1–50 mg. of material are available, is illustrated by Hinton's (1944) study of wheat grains in which 59% of the aneurin is localized in the scutellum.

As early as 1919, Williams suggested the use of yeast-growth as a means of assay of aneurin. Two microbiological methods may be considered sufficiently reliable to warrant mention: (a) the growth of *Phycomyces blakesleeana* (Schopfer & Jung, 1937; Meiklejohn, 1937; Sinclair, 1938, 1939); (b) the fermentation of yeast (Atkin, Schultz & Frey, 1939). The growth of phycomyces is extremely sensitive to minute amounts of aneurin and, at present, it provides the only satisfactory means we have for gauging the level of aneurin in blood. To appreciate its limitations, the various papers of Sinclair (1938, 1939) should be consulted. Equally sensitive is the method of Atkin *et al.* (1939). It is based on the measurement of the rate of fermentation of sugar by yeast, using a Warburg or similar apparatus. With flours and bread it gives results as good as those obtained by other methods.

Riboflavin: This vitamin has a yellow-green colour and an intense yellow-green fluorescence. This property has been used in several methods for the determination of the vitamin. Yet fluorimetry does not appear to have gained the favour that investigators have bestowed upon the microbiological method. This is probably because no easy means have yet been found which, at the same time, effect a concentration of the vitamin and separate it from the substances interfering with its fluorescence. From the success which has attended the use of non-aqueous solvents and adsorbents in the isolation of riboflavin from urine (Najjar, 1941) and wheats, bread and milk (Barton-Wright & Booth, 1943), a more extensive use of the fluorimetric method is predictable.

At the moment, the microbiological method seems the more hopeful, and comparison of results with those obtained by biological methods, shows that they are almost as reliable. *Lactobacillus casei* is the organism ordinarily used. Under carefully standardized conditions, the growth of the organism is proportional to the concentration of riboflavin, and can be measured by titration of the amount of acid formed by the organism. Applied to the assessment of the daily intake of riboflavin of military personnel and workers, the method has shown that the daily consumption of riboflavin approaches 2 mg.

Nicotinic acid: Most chemical methods for the estimation of nicotinic acid are based upon König's reaction. The product of the rupture of the pyridine ring is condensed with a primary aromatic amine (aniline, *p*-aminoacetophenone, metol), to give a polymethine dye (Melnick & Field, 1940; Harris & Raymond, 1939; Kodicek, 1940; Bandier, 1939). The methods are considered specific for nicotinic acid; pyroxidin, another pyridine compound, does not give König's reaction. Natural pigments are a source of interference with the measurement of the coloured dye, and in plant-materials erroneous results arise from chromogens and pyridine-like substances. The method has permitted a much wider survey of the distribution of nicotinic acid in foodstuffs than the biological tests, for which the dog is the most suitable animal.

Application of the method to blood, where the greater part of the vitamin is in the erythrocytes, suggests that the level of nicotinic acid is not a good criterion of nutritional status (Carter & O'Brien, unpublished observations). In

fact, little difference has been found in the blood nicotinic acid of normals and pellagrins. It is possible that a more suitable means of studying nicotinic-acid deficiency lies in the estimation of nicotinamide methochloride (Najjar & Wood, 1940; Huff & Perlzweig, 1943; Ellinger & Coulson, 1943). The elimination of this substance in the urine is dependent upon the amount of nicotinic acid in the diet, although it may also be related to the availability of methyl donors in the body (Ellinger & Coulson, 1944). In general, the results of the chemical and microbiological methods are in agreement. *Lactobacillus casei* and *Lactobacillus arabinosus* are preferable to other organisms for the assay of free nicotinic acid. While improvements are still being made in the medium to enhance the response of the organisms to nicotinic acid, it is inadvisable at present to recommend any particular technique.

Pyroxidin : Pantothenic acid : There is no strong evidence pointing to an important rôle in human nutrition of either pyroxidin or pantothenic acid, although the detrimental effects of their absence from the diet of the rat are well established. Only a brief mention of some of the methods used in their determination will therefore be made. In virtue of its phenolic group, pyroxidin gives a blue colour with di-halogen quinone chlorimides, due to the formation of indophenols (Scudi, Koonen & Keresztesy, 1940). On this reaction is based a method of estimation which has been applied to foodstuffs. Microbiologically, pyroxidin can be assayed by its growth-promoting effects upon *Lactobacillus casei*, *Saccharomyces cerevisiae* (Williams, Eakin & McMahan, 1941), or the mould *Neurospora sitophila* (Stokes, Larsen, Woodward & Foster, 1943). Modifications have been necessary to obtain better agreement between these tests and the biological tests when they are applied to natural materials. It cannot be said that the tests have reached their final forms.

It is too early to judge the value of the methods of assay of pantothenic acid. Its identification as one of the growth-factors of yeast naturally suggested that its growth-stimulating power upon bacteria would provide a suitable means for its assay. For this purpose *Lactobacillus casei* has been employed for the measurement of the pantothenate content of tissues and foodstuffs. In blood, pantothenate would appear to exist in a free condition and also bound to protein, from which it must be freed by acid hydrolysis to be rendered available for microbiological estimation.

Ascorbic Acid

Plants can synthesize ascorbic acid with remarkable ease. So far no bacterium has been found which requires vitamin C for its growth. This vitamin can be estimated by several chemical methods, which draw upon the reduction of dyes. It was Zilva (1927) who first found that certain concentrates of the vitamin reduced phenolindophenol. But it is upon Tillmans' (1930) observation that the capacity of foodstuffs to reduce 2 : 6 dichlorophenolindophenol ran roughly parallel to their antiscorbutic potencies, that present methods are based. The method consists in titrating the vitamin-C extracts, usually made with metaphosphoric acid, with Tillmans' dye, and it has been used to determine urinary elimination of the vitamin and its level in plasma and leucocytes. Most of these determinations have as their object an assessment of the nutritional status of the individual as regards vitamin C. Although they have given valuable information, still further knowledge is required, not only for their proper interpretation, but also for their absolute evaluation.

Since the time of Tillmans' discovery, numerous modifications of the dichlorindophenol method have been made to render it more accurate in the ascorbic-acid assay of foodstuffs. The chief object of most of them is to circumvent the interference of other substances which reduce the dye. Among these compounds are iron and stannous salts, sulphides and thiosulphates. More important are biological compounds like cysteine and certain ene-diols, including reductones and reductic acid, which, in their chemical behaviour, are difficult to distinguish from ascorbic acid. These substances occur in caramelized and fermented products. Reductone can be produced by alkaline treatment of glucose and other sugars. The formation of this substance may not occur when foodstuffs are heated, but other substances of a "reductone" type

may arise when sugar is heated to a pH of 5.4, and in dehydrated foodstuffs submitted to heat treatment.

For some time after Tillmans' introduction of 2 : 6 dichlorophenolindophenol, doubt of the reliability of dye methods lay buried beneath the abundant evidence of the good agreement between this chemical method and the animal tests upon a variety of foodstuffs. It is now clear that in many commercial products due allowance must be made for reductones and like substances. An interesting observation of Lugg (1942) of Australia suggests a possible means of differentiation between ascorbic acid and other indophenol-reducing substances by their different rates of reaction with formaldehyde at different pHs. Mapson (1943) introduced a modification of the above procedure with the object of dealing particularly with the elimination of reductones. Lugg's principle has been under critical observation by Snow & Zilva (1943, 1944), who point out its limitations when applied to the estimation of ascorbic acid.

A note on the method of ascertaining the end of the oxidation of the dye-stuff with ascorbic acid is perhaps worth while. This may be achieved by usual observation of the end-point in the titration of dye with vitamin, or photometrically, or electro-chemically. The last has the advantage of permitting titration to be made with coloured fluids.

Another complication to be considered in estimating ascorbic acid lies in our ignorance of the amount of dehydro-ascorbic acid in tissues. In fresh fruits, vegetables, blood and urine, dehydroascorbic acid has been considered to be present in negligible quantities. It has usually been estimated as ascorbic acid in materials which have been gassed previously with hydrogen sulphide. This reductive procedure is not very attractive. It is tedious and creates false values for dehydroascorbic acid by the formation of additional reducing substances. Dehydroascorbic acid, however, yields an hydrazone with 2 : 4 dinitrophenylhydrazine. Roe & Kuether (1943) have applied this reaction to the determination of dehydroascorbic acid and ascorbic acid in blood and urine. Compared with other methods, Roe's procedure gives similar results for ascorbic acid. In fact, the method gives the same result as the titrimetric and the photometric, from which it would appear that pyruvic acid and glucose interfere only slightly (Higgins & O'Brien, unpublished observations). Blood and urine lack the complexity of plants and processed materials, in which reductones and other interfering substances are found. This may impose a limitation to a general application of Roe's method.

Vitamin A

In addition to biological assay, two methods, one physical and the other chemical, are in general use for the estimation of vitamin A. Introduced by Drummond & Morton (1929), the physical method has as its basis a property of vitamin A concentrates, namely a selective adsorption in the ultraviolet band with a maximum at 328 m μ . Its accuracy is well attested by many workers, but hardly compensates for the time which its intricate and expensive apparatus demands for an estimation. Accordingly a preference has developed for colorimetric and photometric methods. Pursuing the observations of Rosenheim & Drummond (1925), who showed that vitamin-A-rich oils gave colours with arsenic trichloride and trichloroacetic acid, Carr & Price (1926) found that a blue compound was formed by such oils and antimony trichloride in chloroform. This colour, which is due to a light-absorption at 617-620 m μ and 580-585 m μ , could be matched with the standard glasses of the Lovibond Tintometer.

The Carr-Price reaction led to the development of several comparative methods. They are all open to errors, whose sources lie in differences between the light-absorption of (a) the colour standard or glasses and (b) the unknown; the difficulties of visual matching; non-linear relationship of the vitamin A concentration and readings, and so on. They have a further weakness in that they do not permit that speed of manipulation so necessary for dealing with the rapid fading of the blue colour.

The introduction of the photo-electric absorptiometer of the type designed by Evelyn, Yudkin and others, has removed several of the objections of the colorimetric methods. The

photo-electric absorptiometers have advantages in the speed at which measurements can be made, and in an objectivity which eliminates the personal factor. Their applicability can be extended by the choice of filters. By the use of filters isolating a narrow spectral band coincident with that of the maximum absorption at 620 m μ of the blue colour of vitamin A and antimony trichloride, or with that of the yellow colour of carotene, both substances can be estimated in the same oil or extract. The sensitivity of such instruments is such that determinations on 3 ml. of plasma are possible with an error of $\pm 5\%$.

With blood plasma, it would appear inadvisable to free the carotenoids by preliminary alkaline hydrolysis. This treatment causes low results, probably on account of destruction of the polyenes. Ether-extraction of the plasma after precipitation with alcohols ensures also complete removal of the carotenoids. The yellow petroleum ether extracts are then used for the determination. Even when great care is taken in the preparation of antimony trichloride reagent, and in rigid standardisation of the conditions of estimation, fading of the blue, with the small amounts of pigments in the extracts, constitutes a problem. Urban, Milder & Carruthers (1943) recommend that photo-electric measurements of blue colour of vitamin A and carotene with SbCl₃ should be made at 0°, a temperature at which the rate of fading is considerably reduced. From a study of the rate of fading, Hoch (1943) has been able to apply corrections to his values for vitamin-A concentration. By photographing the reaction-mixture with light of a selected wave-length range, he was able to measure the antimony-trichloride : vitamin-A colour within 2 seconds of the addition of the reagent to the vitamin. In this way it is possible to analyse the carotene and vitamin content of 0.1 ml. or less of serum—the amount obtained with a finger prick. This method may prove valuable in vitamin-A estimations upon the blood of infants or small animals.

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¹ [see BMB 493]

² [see BMB 494]

Vitamin D

In the case of other fat-soluble vitamins, among which the vitamins D rank first in importance, no particular methods of determination have gained general approval. Bio-assay still remains the most reliable means of determining the antirachitic potency of natural products. Nevertheless physicochemical technique combined with chromatography may resolve many of the obstacles to the development of a method more rapid than, but as satisfactory as, the biological. The amount of vitamin D is highly variable in oils and, with all of them, particularly the less potent, a preliminary step in most methods has been a concentration of the vitamin in a non-saponifiable fraction. With such fractions, spectrophotometric and colorimetric analyses are vitiated by the presence of sterols, such as cholesterol or 7-dehydrocholesterol, and of vitamin A. Of several colour reactions for vitamin D, the one with antimony trichloride is most promising. Especially is this the case when the reagent is prepared by the solution of anhydrous SbCl₃ in purified chloroform to which has been added acetyl chloride. As little as 2 μ g. of vitamin D added to this mixture produces a yellow colour with a maximum absorption at 500 m μ .

The reaction has been used by Ewing, Kingsley, Brown & Emmet (1943) in a procedure of some interest. By chromatographic adsorption upon superfiltrol, the vitamin D and sterols are freed from vitamin A; a second chromatographic adsorption separates vitamin D from the sterols. Determinations of the extinction coefficient, $E_{1\text{ cm}}^{1\%}$, at 500 m μ for the products of reaction of the mixture of sterols plus vitamin, and of the sterols alone, yield values from which the vitamin-D concentration can be computed by difference. Despite its lengthy procedure, the method gives results in agreement with those of biological assay. It does appear to represent real progress towards a method satisfactory for the analysis of oils and of natural and fortified milks.

SOME PRINCIPLES OF WAR-TIME FOOD POLICY

MAGNUS PYKE, PH.D., F.R.I.C.

Scientific Advisers' Division, Ministry of Food, London

When Great Britain was involved in war in 1939, the first plans of the Ministry of Food at that time tacitly assumed that supplies of the foods then being eaten would continue and that, subject to the guarantee of a minimum share of those items which were scarce, the public could be left to choose its own diet. Very soon, however, it became apparent

that some more rational food policy would have to be adopted and only a few weeks before the fall of France an intelligent plan was drawn up based on nutritional principles. The broad scientific basis of this plan has remained unshaken throughout the war. That is to say, the national diet, whether derived from home-grown items or from imported

commodities, has been based on the provision of food calculated to allow sufficient nutrients per head of the population for adequate health, with a free carbohydrate intake to supplement individual needs.

We now can draw up a table showing the average needs for each of ten or twelve separate nutrients for each different class of individual making up the population. Furthermore, it is possible to compile a table showing the nutrient composition of the foodstuffs which enter into the national diet. Thus, on the basis of these two lines of approach, an adequate food policy can be established. In considering this policy it is, perhaps, easiest to take each of several nutrient factors separately.

Calories

The energy value of a diet, expressed as calories, is in some respects the nutrient concept of most fundamental importance. To say that a man is not getting his calorie needs is to say that he is hungry. People can live for a very long time with too little to eat, but they will suffer. Muscular efficiency, and with it the capacity for industrial work, will be affected. The alertness and vigour of the population will decrease and there will be a loss of weight.

All foods provide energy for the body. The staple energy-foods are, however, cereals and potatoes, although, owing to the high proportion of water in potatoes, bread is, weight for weight, three times as good a source of calories. In the same rank as cereals comes sugar. Finally, more than twice as concentrated as any other food, fats are the richest of all sources of calories.

As the physiological need for calories is dependent on the amount of physical work a man does, and as the requirement immediately changes if an individual finds himself, if only for a short period, doing work of unaccustomed activity, the strict rationing and control of calories is difficult. The British policy has been, therefore, to provide for an unrestricted consumption of bread and potatoes. The Germans were forced to introduce a complicated rationing scheme for calories at an early stage in the war, principally because their nutritional position was less secure than that of the British. There is always an element of danger in a food plan when people do not have a cheap and unrestricted supply of an "energy" food.

Two periods in war-time food administration in the United Kingdom throw an interesting light on the national calorie consumption. Although cheap bread and potatoes have always been available in the shops, there is little doubt that, during the winter of 1940 and the early spring of 1941, people tended to eat food of insufficient calorie value and in those cases there was a loss of weight. This under-consumption of food was due to the fact that the diet was, although reasonably adequate nutritionally, uninteresting and lacking in variety. When more variety could be introduced, following the passage of the U.S.A. "Lend-Lease" enactment, the situation improved. The second period of strain on the calorie situation came about a year later. At this time, the shipping situation had become so serious that the possibility of not being able to continue to allow unrestricted bread consumption had to be faced, and a detailed plan for bread rationing was worked out. Fortunately the supply position improved and this fear was dispelled.

A number of expedients have been adopted during the course of the war to maintain the supply of calories. As animals can never produce the amount of food equal to the calorific value of the crops which might be grown on the same area, extensive tracts of country were ploughed up and wheat and other cereals which could be used in bread were grown on them. A large increase also occurred in the production of potatoes. Between 1938/39 and 1942/43, it was estimated that the increase in home-grown calories amounted to 30%. Similar in principle to the transfer of land from the feeding of animals to the direct feeding of men, was the use for human food of a proportion of grain offals normally used as fodder. Before the war, 72% of the wheat was extracted in the production of flour. Immediately the war began, the extraction was increased to 75%. At the end of 1941, however, when Japan made her attack, it was decided to use 85% of the grain for human food.

In parallel with the changes made to increase the production of calories at home, great efforts were made to import calories economically from abroad. By June, 1943, although the amount of foodstuffs imported had been reduced by

50% the amount of calories imported was reduced by only 15%. This result was largely achieved by a heavy reduction in the tonnage of animal feeding stuffs imported, and the choice of more concentrated items in place of bulky foods such as fruit. Meat was imported boneless or canned, and milk and eggs were brought in the dried state.

Fat

The amount of fat available in the diet has an important bearing on calorie consumption. Fat is the most concentrated of all sources of energy; when there is a shortage of fat, it is inevitable, therefore, that the bulkiness of the day's food must increase. Dietary fat can be classified under two heads: "visible" fat can be said to comprise such things as butter, margarine and cooking fat; "invisible" fat will include the cream in milk and the fat in bacon and meat. During war-time, fat is hard to get and it may be advisable to sacrifice "invisible" fat in order to maintain a reasonable supply of "visible" fat for cooking and other purposes. In Britain, butter, margarine and cooking fat are rationed, and it has been possible to keep the total ration steady. But, while it has not been found necessary to go to the length adopted by the Germans, who have to skim their milk in order to maintain supplies of butter, a certain amount of "invisible" fat, mostly from meat, has been used to increase the supplies of "visible" fat.

The total amount of fat, "visible" and "invisible," available per day per head of the population was calculated to be 131 g. before the war. At the end of 1940, the figure had fallen to 115 g. and, by the second quarter of 1941, it had reached 104 g. per head per day. This was one of the worst periods of the war with respect to food supplies. By the end of 1943, the figure for fat was about 111 g. It can thus be seen that the reduction in total fats in the diet amounted to 21% in 1941 and that the more recent figures represent a 15% reduction on the pre-war level. As one of the most important nutritional functions of fat is to provide calories in a compact form, it is very difficult to fix scientifically a minimum for the national diet, as a reduction in calories from fat could be made good by an increase in calories from, say, bread. The figures for fat consumption given above, in fact, represent more than 30% of the diet's calories, which is a value sometimes thought to be physiologically desirable. It is, however, true that, when the amount of fat fell as low as it did in 1941, the diet became correspondingly unpalatable and bulky. This bulkiness may, under some circumstances, be crucial. For example, children who have high calorie needs and comparatively small stomachs may not be able to eat an adequate diet, even if it is put before them, if it is unduly bulky. For this reason, the allocation of fat permitted by the Ministry of Food for school meals has always been greater than that permitted for any other type of catering.

Protein

"If you look after the calories, protein will look after itself." This remark of Starling's is broadly true when the total protein in the diet is considered. It is true because, in war-time, almost every food contains a proportion of protein sufficient in the aggregate to give 1 g. of protein per kg. of body weight, which is usually accepted as a rough guide to an adult's needs.

A fraction of the total protein supply which is of especial physiological importance is that derived from animal foods. In the pre-war years, a steep gradation existed in the amounts of the most important sources of animal protein, milk, meat and even cheese, eaten by the rich and by the poor. The Ministry of Food imposed a uniform ration of meat, bacon and cheese for the whole adult population. Milk and eggs were also distributed as evenly as possible to adults. In order, however, to provide mothers and young children with an increased supply of animal protein, for which they have a specific physiological need, a priority allowance of milk was made under the National Milk Scheme for these groups. A prior claim on eggs was also established. An important aspect of milk distribution was a great expansion of the "Milk in Schools" scheme. These measures were aimed to distribute the available animal protein evenly over the population, except in the case of those individuals whose physiological needs demanded more.

By the beginning of 1941, however, national supplies of animal protein seemed almost inadequate for the national needs. When, therefore, the U.S. were able to offer a choice

of food under Lease-Lend, an urgent request was made for supplies of canned meat and fish, cheese, dried milk and dried eggs, all of which were intended to stabilise the situation in respect to animal protein.

Calcium

One of the most consistent deficiencies in the pre-war British diet was a shortage of calcium. Much of this shortage was due to disparities in the consumption of milk and, indeed, to the consumption over the country as a whole of too little milk. In the years immediately before the war attempts were being made to increase the total amount of milk drunk, and it was the deliberate policy of the Ministry of Food to continue these efforts even during the difficult war-time period. Since 1939 the total consumption of liquid milk has risen 28 %. Because of the organization of general distribution, and because of the priority claims of expectant and nursing mothers and of children, the consumption among some sections of the wealthier has fallen, but there can be no doubt that the operation of these plans has tended to improve the nutrition of the country as a whole. It has certainly effected a general improvement in the figures for calcium intake.

Subsidiary to the emphasis on milk as such, there has been a recognition by the Government of the nutritive importance of cheese and dried separated milk. These products not only provide good protein but are also sources of calcium and riboflavin. Every effort has been made to introduce the maximum proportion of these foods into the diet. The distribution of cheese is principally made by means of the standard ration equal for all. Part of the dried separated milk supply is directed to children, who have high calcium needs, by encouraging its use in the preparation of school meals. It is also distributed as *National Household* milk to hospitals and other institutions.

Perhaps the most important step to improve the calcium content of the diet has been its incorporation, as chalk, in bread. One of the disadvantages of extracting, in the process of milling, an increased proportion of the grain for human consumption, is that the amount of phytic acid present in the loaf is increased. Phytic acid is derived from the outer layers of cereal grains and possesses the unfortunate property of rendering a proportion of dietary calcium unavailable to the body. The addition of calcium to *National* flour was calculated to neutralize this effect and to improve calcium intakes. In April, 1942, the Ministry of Food imposed on millers the obligation to add 7 ounces [about 200 g.] of chalk (*creta preparata*) per sack of 280 pounds [about 130 kg.] of 85 % wheatmeal flour. This addition represents a supplement of about 180 mg. of calcium to the average daily intake.

The consumption of green vegetables, which has been so greatly encouraged during the war, also serves to increase the calcium intake.

Iron

The restriction in supplies of meat might have been expected to reduce still further the deficiency in iron among poorer people. The first step to prevent such an occurrence was the uniform rationing of available meat. Next, the change in the character of the bread caused an increase in supplies of dietary iron, and, finally, an increased consumption of green vegetables did the same. The introduction of 85 % extraction flour made a substantial addition to the iron content of war-time diets. This *National Wheatmeal* contains about 10 mg. of iron per pound [about 0.454 kg.], whereas the pre-war type of white flour contained about 5 mg. per pound.

Vitamin A

Although a great deal of research has been done on vitamin A since its discovery in 1913, it is not possible to be dogmatic about the quantities required in the diet. It is known, for example, that the dietary allowance need not be so great if all the vitamin A is derived from animal sources and, on the contrary, if the vitamin activity is derived largely from vegetable foods the requirement will probably be more. In spite of this element of doubt as to quantitative needs which, for that matter, extends to other vitamins, it is likely that deficiency of vitamin A was widespread in pre-war British diets. Unfortunately, it has not proved possible entirely to rectify the situation. Several steps have been taken to provide vitamin A in the war-time diet. The vitamin has

been incorporated in margarine to the extent of about 500 international units per ounce [about 28 g.]. The encouragement of the consumption of green vegetables has in part been proposed in order to increase the intake of vitamin A. Among the best vegetable sources of vitamin A is, however, the carrot, and the production of this vegetable has consistently been increased and its consumption encouraged. Another source of vitamin A to which special attention has been directed is dried egg, which has been a notable war-time development. All these foods are intended to maintain the diet of the adult population. Young children, however, cannot be expected to eat large amounts of green vegetables and carrots. For those below the age of 5 a special issue of cod-liver oil has been made available. This oil, put out by the Ministry of Food, has a minimum vitamin A content of 1000 international units per g. Although foodstuffs had previously been distributed to satisfy specific nutritional needs, and in this connection milk-issues and the provision of school meals to necessitous children will be remembered, the provision of a vitamin concentrate such as cod-liver oil to infants and young children is probably the first example of the distribution of a specific nutrient without distinction to all those who have a special need for it. Besides young children, pregnant and lactating women have been provided with a national issue of a vitamin-A concentrate.

Vitamin B₁

Early in the war there was a proposal to add synthetic vitamin B₁ to flour in order to overcome a bad deficiency in the pre-war diet of the poorer people. This plan was being put into effect when, early in 1942, the shipping situation became so threatening that it became necessary to raise the rate of extraction of flour to 85 %. The result of this change in milling practice was to increase markedly the vitamin B₁ of the national diet. Vitamin B₁ is concerned in the utilization of carbohydrate in the body. In peace time there are two important carbohydrate foods which do not contain within themselves sufficient of the vitamin for their own utilization and which thus combine to cause a net deficiency in the diet. These are white flour and sugar. Under war-time control, the amount of sugar in the diet was radically restricted, and the change in milling practice now converted flour from a vitamin B₁ liability into an asset. *National wheatmeal* (85 % extraction) contains approximately 1.3 mg. of vitamin B₁ per pound, as compared with pre-war white flours with about 0.5 mg. per pound.

Vitamin C

As a result of the shortage of ships in 1940, it was decided to dispense with imports of fruit, which form a bulky and wasteful cargo, and to depend, instead, for vitamin C on potatoes and other vegetables. The area of land available for vegetable production was, of course, limited and, while considerations such as hardness to the weather, cropping season, perishability and national taste were given some degree of weight in planning the type and amount of the vegetables to be grown, the principle which finally influenced the acreage for any vegetable was the nutritional value of each crop.

Vegetables are perishable commodities and the yield from them often varies widely from season to season. It is, therefore, very difficult to regulate their distribution with any degree of precision. In order to implement the nutritional policy of depending on potatoes and green vegetables for vitamin C and a proportion of vitamin A, the Government of the United Kingdom controlled prices. In addition, however, they gave every encouragement to the domestic production of vegetables in gardens and allotments. Much publicity and quite detailed instructions were issued so that the individual gardener might make the best use of what little land was available to him. These domestic instructions, in parallel with the national directions to the farming community, were devised to produce supplies of vitamin C and vitamin A all the year round.

Vegetables, while they can provide adequate amounts of vitamin C in the diet of an adult, must be eaten in comparatively large quantities if they are to do so. They are not, therefore, suitable as the sole sources of the vitamin for infants and young children. In order to supply this nutrient for children under 5 years old, a scheme was put into operation in 1940 for using a substantial proportion of the national crop

of blackcurrants [*Ribes nigrum*], which are fruit exceptionally rich in vitamin C, for the preparation of a syrup for distribution as a ration to children. In the following year, concentrated orange juice, which was received from America under Lease-Lend, was substituted for blackcurrant syrup: These vitamin-C concentrates were issued to expectant mothers as well as to young children.

Vitamin D

Vitamin D is of special importance to expectant and nursing mothers, infants and children. As milk is one of the foods containing vitamin D, the allocation of milk to these groups of the population helps to provide part of their needs. Vitamin D is present in butter; at the beginning of the war it was, consequently, put into margarine at the level of 1 international unit per g. Later, in 1941, when eggs, which are also good sources of vitamin D, became scarce, the amount added to margarine was doubled to 2 international units per g. It has remained at that level, although the egg situation was improved by the importation of dried egg.

Besides the supply of vitamin D from foodstuffs, it was decided to make special provision of the vitamin for mothers and infants in the form of a standardized preparation of cod-liver oil. The original specification was 100 international units of vitamin D per g. Later, this was raised to 200 international units per g. More recently, in an effort to increase the proportion of women taking advantage of these supplements, an alternative issue to pregnant women has been in the form of tablets each containing 4000 international units of vitamin A, 800 international units of vitamin D and 250 mg. of calcium phosphate B.P., the recommended dose being 1 daily.

Communal Feeding

Communal meals have proved to be an essential adjunct to the country's nutritional policy. Their first importance appeared at the end of 1940 and the beginning of 1941, when many of the cities of Britain first came under heavy bombardment. The *British Restaurants* which were developed at

that time are still of importance for providing meals in places to which large populations have come as the result of the war, and also to feed people in towns where domestic life may have been made difficult or where catering facilities are inadequate.

Hand-in-hand with communal meals intended for the population at large, has been the development of meals in factories. The importance of industrial restaurants was realized early in the war and in 1940 the Ministry of Labour issued an order, compelling all firms which employed more than 250 people and which were doing war work to establish an adequate restaurant. Within two years, more than 8,000 factory restaurants were set up. There are now over 16,000. Before the war there were only between one and two thousand industrial restaurants. Finally, out of the total 4½ million of the nation's schoolchildren, about 1½ million receive hot school-meals.

Food is allocated to restaurants, in proportion to the number of meals served, in a manner similar to the general system of distribution. Rations, "points" and, for milk, eggs and some other foods, controlled supplies, are made available. The amounts of food provided, however, are not equal for all types of restaurants but are varied in accordance with nutrition policy. Three levels of allocation have been fixed. *British Restaurants* receive amounts equal to those permitted for commercial restaurants and hotels; factories where moderately active work is done get more, and very heavy workers receive more still. The physiological needs of children are in many ways proportionally greater than those of adults; the allowances to school restaurants are, therefore, the largest of all. Besides rationed food, restaurants can, of course, buy what they please of bread, potatoes, vegetables and other items, the supplies of which are unrestricted.

In a short article such as this it is impossible to go into the full detail of all that has been done to guide Britain's food policy during the war. It is, however, perhaps fair to say that from all points of view, whether it be economy in transport or the health and well-being of the population, the application of scientific nutritional principles to the national administrations has in general been amply rewarded with success.

REVIEW OF SELECTED PAPERS

Assay of Vitamins in Food and Body-Fluids

493

THE VITAMIN B₁ CONTENT OF NATIONAL FLOUR AND BREAD—THE RESULTS OF COMPARATIVE TESTS BY VARIOUS METHODS: With an Appendix on the Thiochrome Method for Estimating Vitamin B₁ in National Flour and Bread

by R. A. Peters, H. Chick, K. H. Coward, L. J. Harris, B. S. Platt & T. F. Macrae, *Biochemical Journal*, 37, 433-439, September 1943

The writers of this paper comprised the Vitamin B₁ Subcommittee of the Accessory Food Factors Committee, appointed jointly by the *Medical Research Council* and the *Lister Institute*. The vitamin-B₁ content of 85%-extraction flours and of the bread made from one of the flours was determined by 15 laboratories and groups of investigators, in order to compare the merits of chemical with those of biological and microbiological assays. The bread was baked in a batch of forty loaves of two pounds [about 0.9 kg.] each by a usual commercial procedure. The loaves were sliced a few hours after baking and the slices were placed on slatted shelves and dried at 37° C. Drying was complete in two days, when the whole was powdered in a mill.

The biological methods used were the rat-growth method (Chick & Roscoe, 1929; Harris, 1940-1), the rat-bradycardia method and the "cure of convulsions" method

(Harris, 1940-1). The microbiological method was that of Schultz, Atkin & Frey (1942). The chemical methods used were the thiochrome method [see below] and the azo method (Platt & Glock, 1943). All methods of estimation gave values which were in good agreement, especially for the flours. The chemical tests appeared to show a loss of the vitamin on baking, but the biological tests were not accurate enough to confirm this. No distinction was possible between the accuracy of the visual method as opposed to the photo-electric method in the determination of thiochrome, nor was the azo method more accurate than the thiochrome method. National flour (85% extraction) contains between 3 to 4 µg. vitamin B₁ per g. of dry flour.

Appendix

Two methods for estimating vitamin B₁ in national flour and bread are described in detail. The method employing a visual comparison of fluorescence is based on that of Harris & Wang (1941) and Wang & Harris (1942). The photo-electric method is that of Booth (1940, 1942). Flour or bread is heated with 0.02N hydrochloric acid on a boiling water-bath for 10 minutes, sodium acetate-acetic acid buffer (pH 4.0) is then added, the mixture cooled to 40° C., brought to pH 4.0 and digested with takadiastase and papain for some hours. Fluorescent impurities are removed by washing with isobutanol at pH less than 4.0. The vitamin B₁ which remains in the aqueous layer is oxidized to thiochrome, a blue fluorescent substance, by potassium ferricyanide in the presence of methanol and excess sodium hydroxide. Simultaneously an equal volume of the flour extract is treated in

the same way, but without the addition of potassium ferricyanide; this forms the blank. A third flask is also set up containing a known amount of vitamin B₁ which is converted to thiochrome.

After treatment with hydrogen peroxide, the fluorescent material is extracted with isobutanol, the extract washed with water and clarified by the addition of ethanol. Equal volumes of the isobutanol extract of the "unknown" and the "blank" are compared visually in front of the Wood's glass window of an ultraviolet lamp. The standard "control" isobutanol extract is added to the "blank" from a graduated pipette until the fluorescence observed on looking down the tube matches exactly that of the unknown. The tubes are mixed by inversion and, before the final matching, a volume of isobutanol equal to that of the "control" isobutanol extract added to the blank is added to the unknown. The use of a Wratten 18A filter with the Wood's glass reduces errors due to substances with fluorescences of tints other than the purplish-blue tint of thiochrome. The matching must be effected rapidly.

When the Spekker fluorimeter is used, the standard should be stronger than the unknown. Because thiochrome is relatively unstable in ultraviolet radiation, 1 µg. quinine sulphate per ml. 0.1N sulphuric acid is used as the standard solution. The instrument is calibrated against the quinine standard by means of a series of aneurin standards, which have been prepared by oxidizing standard solutions of aneurin with precisely the same technique as is employed for flour or bread.

Identical laboratory conditions, particularly as to temperature, should be secured for the conversion of vitamin B₁ to thiochrome in both standard and unknown solutions. Test-tubes used in the visual method must be of non-fluorescent glass and identical in shape and of uniform diameter. To avoid the addition of fluorescent impurities, solutions must not come into contact with "unextracted" corks, rubber or tap grease. Glass-distilled water should be used. Solutions of thiochrome should be kept away from bright light and comparisons of fluorescence should be made in a darkened room.

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[see BMB 494]

494

AN AZO COLOUR REACTION FOR THE DETERMINATION OF VITAMIN B₁ IN NATIONAL FLOUR

by B. S. Platt & G. E. Glock, *Biochemical Journal*, 37, 439-443, 1943

This method which, with minor modifications, can be used for the estimation of pure vitamin B₁, has been devised by two whole-time members of the staff of the *Medical Research Council* working in the Nutrition Building of the *National Institute for Medical Research*, London. Flour (25 g.) is extracted with 0.5N hydrochloric acid (100 ml.) for several hours, stirring at intervals and allowing to stand overnight. All the vitamin passes into the aqueous phase, and is separated by decantation and filtration through a No. 1 Whatman filter paper. 40 ml. of the filtrate are run into a 150 ml. glass-stoppered bottle, 50 mg. of "Superfiltrol" (activated clay) are added and shaken for 30 minutes. The contents of the bottle are transferred to a 50 ml. centrifuge tube, the bottle being washed out with 5 ml. 0.5N hydrochloric acid.

Centrifuge until the clay is well packed, pour the supernatant fluid back into the bottle and repeat with another 50 mg. clay. Transfer the clay quantitatively to the centrifuge tube, discarding the supernatant fluid after centrifugation and wash the bottle with five successive portions of 5 ml. 0.5N hydrochloric acid. Resuspend the clay in the washings, centrifuge and discard the supernatant liquid. The washed adsorbate is suspended in 1 ml. distilled water, 2 drops of bromocresol-green are added and the pH is adjusted to 5 by addition of 2% sodium hydroxide.

The suspension is transferred to a 25 ml. glass-stoppered cylinder. Wash the centrifuge tube with five successive portions of 2 ml. 60% ethanol, adding the washings to the cylinder. 2 ml. of 3% sodium bicarbonate in 0.6N sodium hydroxide in a dry test-tube are treated with 2 ml. of diazo reagent. The diazo reagent is prepared by adding 1.5 ml. 4.4% sodium nitrite solution to 1.5 ml. 0.8% *p*-aminoacetophenone in 3.5% hydrochloric acid, both solutions having been cooled to 0-5° C. and kept at that temperature for 10 minutes, when a further 6 ml. sodium nitrite solution is added.

The solution is made up to 50 ml. with ice-cold distilled water and allowed to stand at least 15 minutes before use. It is prepared on the day of the test and must be kept at 0-5° C. After addition of the diazo reagent, mix by inverting, and exactly 1 minute later add to the suspension of the adsorbate in the cylinder. Mixing is effected by inversion every few minutes. After 20 minutes, 5 ml. of toluene are added and mixing by gentle inversion is continued at frequent intervals for a total period of 1 hour. The toluene layer is transferred to another stoppered cylinder containing 10 ml. 0.5N hydrochloric acid and washed by inversion. The toluene layer is then transferred to a 5 ml. centrifuge tube, a small amount of anhydrous sodium sulphate is added, the contents are mixed and rapidly centrifuged.

A standard solution is prepared by adding 1 ml. of a diluted standard vitamin B₁ solution to a second washed adsorbate, adding 2 drops of bromo-cresol-green indicator and proceeding as described above, except that 10 ml. of toluene are used to extract the dye. The two solutions are compared in a Duboscq type of colorimeter fitted with cups having a stem capacity of 5 ml. For the estimation of solutions of pure vitamin B₁, the preliminary adsorption on activated clay is omitted, but it was found necessary to wait for 60 minutes instead of 20 minutes before extracting the dye with toluene.

495

NICOTINIC ACID AND RIBOFLAVIN IN BEEF EXTRACTS AND CORNED BEEF

by R. G. Booth & E. C. Barton-Wright, *Lancet*, 1, 565-567, 29/4/44

These workers in the Ministry of Food Cereals Research Station, St. Albans, have determined the nicotinic acid and riboflavin contents of meat extracts, meat juices, fresh and corned beef, and samples of beef and pickling liquors, during processing as corned beef. Nicotinic acid was estimated by the method of Kodicek (1940), modified in some instances by the replacement of 0.4 ml. of *p*-aminoacetophenone reagent by 1 ml. of 10% procaine in 10% HCl, in order to obtain a more stable and intense colour. Riboflavin was estimated by the microbiological method of Barton-Wright & Booth (1943).

Five meat extracts contained from 375 to 1,025 µg. nicotinic acid and 15.6 to 25.8 µg. riboflavin per g. Meat juices gave a range of 345 to 615 µg. nicotinic acid per g.; marmite yeast-extract contained 655 µg. nicotinic acid per g. Eight samples of corned beef contained from 8.5 to 33.4 µg. nicotinic acid and 0.7 to 1.85 µg. riboflavin per g. as purchased. Fresh beef (six different cuts), as purchased, contained 46 to 71 µg. nicotinic acid per g. and roast beef sirloin 57 µg. per g. The low content of corned beef is chiefly due to losses by elution during pickling. It is not due to destruction by sodium nitrite, which is used in this processing.

An average "civilian" helping of corned beef—2 oz. [about 60 g.]—would yield 0.85 mg. nicotinic acid. The same serving of roast beef would give more than 4 mg. About 0.05 mg. riboflavin is provided by the corned beef as against 0.25 mg. in roast beef. A teaspoonful of meat extract, as used to make a large cupful of beverage, would have an average of 5 mg. of nicotinic acid and 0.25 mg. of riboflavin.

These results give an entirely new perspective as to the value of meat extracts nutritionally, and challenge the findings that such articles are of negligible food value but useful as flavouring agents and appetizers (*Lancet*, 1908).

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THE RIBOFLAVIN CONTENT OF FOOD SERVED IN ROYAL AIR FORCE MESSSES

by T. F. Macrae, E. C. Barton-Wright & A. M. Copping,
Biochemical Journal, 38, 132-135, 1944

The authors report results of estimations of riboflavin content of total diet, using the method described by Macrae, Henry & Kon (1943) for obtaining from a representative mixed dietary a dehydrated, homogeneous product. From the average daily dry weight of the food served and the estimation of its riboflavin content, it was possible to determine the average daily intake of riboflavin per person. Estimations of riboflavin were performed (i) by the biological technique devised by El Sadr, Macrae & Work (1940) as modified by Copping (1943), (ii) the microbiological method of Snell & Strong (1939) as modified by Barton-Wright & Booth (1943). Experimental details are given.

Results by the biological method were usually rather higher than those obtained by the microbiological method but, in general, agreement was good.

Of the Royal Air Force personnel tested, airmen were found to have an average daily intake of about 2 mg. and airwomen about 1.8 mg. riboflavin. The optimum riboflavin requirement has been estimated (*Committee on Food and Nutrition*, 1941) as 3 mg. for active men and 2.5 mg. for active women. Other findings, however, indicate that these values may be too high. Further, Lyle, Macrae & Gardiner (1944) observed no sign of riboflavin deficiency in R.A.F. personnel stationed in Britain, and this tends to support the view that the riboflavin intake, as determined by the present authors, was adequate. Regular consumption of beer, which has recently been shown to be a surprisingly good source of riboflavin (Barton-Wright, Moran & Sarson, 1943; Hopkins, 1943), would materially supplement dietary riboflavin, but it is estimated that not more than 10 % of R.A.F. personnel are regular beer drinkers.

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A STATISTICAL EXAMINATION OF THE ACCURACY OF VITAMIN A ASSAYS : AN ANALYSIS OF THREE CO-OPERATIVE EXPERIMENTS DESIGNED TO ASCERTAIN THE VALUE OF THE CONVERSION FACTOR FOR TRANSFORMING SPECTROPHOTOMETRIC VALUES INTO INTERNATIONAL UNITS

by J. O. Irwin, *Journal of Hygiene*, 43, 281-314, April 1944

Those interested in biological assays will certainly be conversant with the author's exposition in *Statistical methods applied to biological assays* (1937), in which he reviewed the best methods available at that date. In the article under notice, the author, a member of the statistical staff of the *Medical Research Council*, gives the results of three experiments devised to re-examine the conversion factor of 1600 which had been previously allotted by the 1934 conference on Vitamin A standardization for converting the results of spectrophotometric tests for vitamin A into international units. Three experiments were devised using (i) halibut-liver oil, (ii) a U.S.P. reference oil, and (iii) solid vitamin A 2- β -naphthoate.

A report on the first experiment had already been published (Hume, 1937) providing no support for changing the existing value, but in view of the fact that the results submitted from the different laboratories had been calculated by different

methods, Dr. Irwin here gives the results of a revised calculation. The conversion factors obtained from the three experiments were respectively 1570, 1820 and 1770, and as these did not significantly differ they were consistent with the hypothesis that the same conversion factor holds for all three substances. The results were therefore pooled, and a conversion factor of 1740 with limits of error of 93-107 % or 1620-1860 obtained.

More important to workers in this field of statistics than the actual results, is the opportunity which the analysis has given to the author to discuss and illustrate the greater accuracy in biological and other assay results now obtainable by the improvements which have been evolved in this branch of statistical analysis since his review of the methods existing in 1937.

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APPARENT VITAMIN C IN FOODS

by F. Wokes, J. G. Organ, J. Duncan & F. C. Jacoby, *Biochemical Journal*, **37**, 695-702, 1943

It has long been known that 2:6-dichlorophenolindophenol reacts with a number of substances besides ascorbic acid. During the past three years, these workers in the *Ovaltine* research laboratories have accumulated evidence to show that, under certain manufacturing and storage conditions, the apparent vitamin-C content of foods can become considerably higher than the anti-scorbutic vitamin-C value. They used both the visual dye titration method and the potentiometric method of Harris, Mapson & Wang (1942).

The apparent vitamin C is determined after treatment with formaldehyde at pH 4.5 for 6 minutes, which destroys all the true vitamin C, adding an excess of metaphosphoric acid solution to bring the pH to 1.0 and titrating with the dye-stuff. The total vitamin C is determined with similar timing and rate of addition of dye, without the addition of formaldehyde.

The highest yields of apparent vitamin C are obtained when the materials (potatoes, cabbage, carrots, germinated grains, grass and lucerne) are treated with 2 % (volume/volume) of HCl or H_2SO_4 on a water bath at 90–95° C., or occasionally on a sand bath for upwards of 8 hours. If smaller concentrations of acid are used, the rate of production of apparent vitamin C is much slower. In 0.25 % HCl apparent vitamin C is unstable to prolonged heating. Heating alone, without the addition of acid, produces an increase in the apparent vitamin-C content of malt extract, fruit syrups and other products, which may mask the destruction of true vitamin C if present.

Apparent vitamin C may be gradually formed during storage under normal conditions. The percentage increase in apparent vitamin C is highest at raised temperatures and lowest in nitrogen-filled containers when all but 1-2% of the total moisture has been removed. Apparent vitamin C occurs in cocoa and chocolate from which it is not removed entirely by precipitation of the tannin.

In fresh fruit, usually less than 10% of the total vitamin C occurs as apparent vitamin C, except for unripe walnuts where it may reach 80 %. Prolonged storage, or the heating of fruit juices, may produce a great increase of apparent vitamin C—to form eventually the greater part of the total vitamin C as determined by the visual dye titration. Demerara sugar, some table syrups, molasses and dark beers may contain apparent vitamin C. Whilst the common raw vegetables do not appear to contain significant amounts of apparent vitamin C, it may be produced during roasting and frying and it does occur in such herbs as sorrel and parsley.

Apparent vitamin C is formed as rapidly at pH 4-5 as at pH 1.0 and is best preserved in nitrogen-filled containers kept in the dark, or by use of cyanide. It is destroyed by ascorbic acid oxidase, or by treatment with 0.1 % hydrogen peroxide or sodium percarbonate at 37° C. for 2-3 minutes. It is gradually destroyed by ultra-violet irradiation. A malt extract having a high concentration of apparent vitamin C but possessing no antiscorbutic action showed a distinct

spectroscopic maximum at about 280 m μ . A discussion of the possible relationship of apparent vitamin C to reductone, reductic acid, dihydroxymaleic acid and hydroxytetronic acid is appended.

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499

ESTIMATION OF "TRUE" ASCORBIC ACID IN URINE

by D. Richter & P. G. Croft, *Lancet*, 1, 802-803, 26/6/43

The method of estimating vitamin C in urine by titrating with dichlorophenolindophenol, developed by Harris & Ray (1935), is liable to error owing to the presence in the urine of sodium thiosulphate and possibly other substances which decolourise the dye. Although a number of modifications of the technique have been proposed to eliminate this error, doubt has been expressed as to whether the figures obtained after their application can be regarded as representing "true ascorbic acid."

The present authors, writing from the *London County Council* Pathological Laboratory and the *Mill Hill* Emergency Hospital, describe a simple and rapid lead precipitation procedure for eliminating the interfering substances in urine which appears satisfactory, and which gives results similar to those obtained by Neuweiler's (1936) ascorbic oxidase method.

In the collection of urine samples it was found that the use of metaphosphoric acid caused much less loss of vitamin C than acetic acid. For most estimations, 2-3 hour samples of fasting urine, or urine after an ascorbic acid-free breakfast, were collected by passing straight into bottles containing 10 g. metaphosphoric acid. Ten ml. of the urine, containing 5 % metaphosphoric acid, were centrifuged after the addition of 1.5 ml. of lead acetate solution (25 % Pb(Ac)₂.H₂O). The precipitate could also be removed by filtering. Samples of the filtrate were titrated for ascorbic acid content by running the dye into the urine (the reverse of the usual procedure). This was done in order to avoid having present during the titration a large excess of dye, which might oxidise substances less rapidly oxidised than ascorbic acid.

The treatment with lead acetate not only removed interfering substances but also some of the colouring matter from the urine, and the end point of the titration was thus easier to determine. There was no loss of ascorbic acid added to the urine as a result of the lead acetate precipitation. Tests in which sodium thiosulphate or quinol were added to the urine showed that they were quantitatively removed by the lead acetate. Other possible interfering substances in urine such as glutathione, catechol, catechin, and sodium thiocyanate added to urine samples in concentrations up to 10 mg./100 ml. did not reduce the dye rapidly enough to interfere with the titration.

The observations made with the lead acetate precipitation method were tested against the ascorbic acid oxidase method. The oxidase was made from cucumbers, cauliflowers or broccoli after the method of Meiklejohn & Stewart (1941). Estimation of the total reducing activity was obtained by simple titration of the urine with indophenol. Then an aliquot portion of the same sample was treated with ascorbic oxidase in the presence of oxygen. Subsequent titrations gave the amount of reducing substances other than ascorbic acid in the treated urine. The difference between the first and second figures gave the amount of reduction due only to ascorbic acid.

The figures for true ascorbic acid obtained by the lead precipitation method and the ascorbic oxidase method agreed very closely.

Aspirin increased the excretion of reducing substances in the urine, but it was not possible to find any evidence as to whether the increase was due to "true ascorbic acid" or to other phenolic reducing substances.

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THE ESTIMATION OF 'TRUE ASCORBIC ACID' IN BLOOD

by D. Richter & P. G. Croft, *Biochemical Journal*, 37, 706-708, 1943

The method which has been evolved by these authors is as follows: 4 ml. of venous blood (showing no hæmolysis and containing 0.3 g. sodium oxalate per 100 ml. blood) are transferred to a 15 ml. centrifuge tube containing 0.05 ml. sec-octanol, and coal gas is bubbled through. 4 ml. distilled water are added and the gassing is continued for ten minutes. Freshly prepared 32 % metaphosphoric acid solution (2 ml.) is added, followed after mixing by 1 ml. 25 % lead acetate solution and 2 ml. saturated sodium acetate solution. After thoroughly mixing, the suspension is centrifuged and 2 ml. portions of the supernatant fluid are titrated with a 0.002 % solution of 2:6 dichlorophenolindophenol which has been standardized against a 0.0005 % solution of ascorbic acid in 2 % metaphosphoric acid. The end-point is reached when a faint pink colour persists for ten seconds and matches a solution made by adding 0.05 ml. of the dye solution to 1 ml. of 1 % metaphosphoric acid solution contained in a similar vessel. In the calculation, the amount of dye added to the blank is subtracted from the burette reading and a correction is made for the ascorbic acid contained in the protein precipitate.

Results obtained using this method agree more closely with those obtained with the ascorbic-acid oxidase method than those obtained without treatment with lead acetate. No significant loss of ascorbic acid occurs in whole blood stored at room temperature, with or without occasional shaking, for 24 hours. The maximum loss in ten specimens was only 22 % in 48 hours. The blood ascorbic acid of 350 normal factory workers in the Birmingham area varied from 0.15-0.85 mg./100 ml. with a mean value of 0.25 during May-July 1943.

Studies on Vitamin C *

501

COMPLEMENT ACTIVITY AND VITAMIN C

by E. Kodicek & B. Traub, *Biochemical Journal*, 37, 456-460, 1943

In recent years conflicting reports as to the correlation of complement activity and vitamin-C intake have been published. The question has been re-examined by E. Kodicek working for the *Medical Research Council* in the *Dunn* Nutritional Laboratory and B. Traub in the Department of Pathology in the University of Cambridge. The end-point of the complement titration was taken as the volume of undiluted serum required to produce a 50 % hæmolysis in a standardized system.

Sheep erythrocytes from a single source were used. Blood samples (2-3 ml.) were obtained by cardiac puncture without anaesthesia, and the serum was diluted 1:30 with 0.9 % buffered saline of pH 7.4. Eight tubes containing different amounts of diluted serum were tested against 0.5 ml. of a suspension of sensitized sheep erythrocytes containing 50 mg. hæmoglobin per ml. After incubation at 37° C. for 30 minutes the tubes were cooled to 2-4° C., 2 ml. of buffered saline added, and after centrifugation the percentage hæmoglobin in the supernatant fluid was determined colorimetrically.

Two series of experiments were made, one during June-July on 22 guinea-pigs weighing 300-368 g., the second during October-December on 18 animals weighing 440-665 g. The basal diet of 11 of the first group of animals was supplemented with 5 mg. of ascorbic acid plus 15 g. cabbage, in the second series supplements of 0.5, 1.0 and 10 mg. of ascorbic acid were given daily. The complement titres of the deficient animals in the summer series ranged from 50-81 units with a mean of 61 units in the second and 63 units in the third week of the diet, whilst those on the supplemented diet were 51-72 units with an average of 60 units. In the winter series the average titre after a daily dose of 0.5 mg. ascorbic

* [see also *BMB* 498, 499, 500, 521, 534, 535, 536, 537, 539, 547]

acid for four weeks was 69 units, which fell to 53 after the supplement had been increased to 10 mg. ascorbic acid daily for five weeks. When the animals had an initial supplement of 10 mg. ascorbic acid daily for four weeks the average titre was 61 units, which became 80 units when the daily supplement was changed to 0.5 mg. ascorbic acid for the succeeding five weeks.

A statistical examination of the results showed without doubt that, when a reliable method of complement titration is used, there is little if any difference between the complement titres of individual guinea-pigs within a group, whether they are maintained on a deficient or optimal vitamin-C diet.

502

SURVEY OF VITAMIN-C LEVEL IN WARTIME IN PREGNANT WOMEN

by A. A. Craig, F. J. W. Lewis & D. Woodman, *British Medical Journal*, 1, 455-457, 1/4/44

This paper, by the Assistant Medical Officer of Health of Bristol and workers in the Department of Preventive Medicine in Bristol University, records the urinary excretion of ascorbic acid, during the 2nd-4th hours after the ingestion of 70 mg. of ascorbic acid per 10 stone [about 64 kg.] body weight, at monthly intervals, in 40 pregnant and 5 non-pregnant women from May 1942 to February 1943. Of the 40 pregnant women, 3 had spongy gums and an anaemia, 6 spongy gums alone, and 8 anaemia alone. Wide fluctuations in the quantity of ascorbic acid excreted were observed, although average values disclosed a significant seasonal variation.

The average value of the urinary ascorbic acid after the test dose for the 5 controls for the whole period (48 tests) was 43.5 mg./100 ml.; whereas that for the 40 pregnant women was 39.7 mg./100 ml. The average excretion of the test dose after the 28th week of pregnancy was slightly smaller than that reached during the first 28 weeks. The authors concluded that the degree of saturation in both groups was low, although during June to October the degree of saturation rose and the diet appeared to be more adequate.

503

THE ASSESSMENT OF VITAMIN-C NUTRITION IN MAN

by F. T. G. Prunty & C. C. N. Vass, *Biochemical Journal*, 37, 623-629, 1943

The need for a reliable and simple assessment of the nutritional status with respect to vitamin C has been emphasized by the importance which has been ascribed to its role in wound-healing and by the possibility of a diminished supply of vitamin-rich foodstuffs in war-time diets. This paper which comes from the Departments of Pathology and Physiology, *St. Thomas's Hospital Medical School*, London, shows that under certain conditions a single determination of the plasma ascorbic acid can be used to assay the standard of vitamin-C nutrition. The report is compiled from the data obtained from 50 subjects (hospital patients and staff) and correlates the results of urinary saturation tests and estimations of plasma ascorbic-acid concentration with an assessment of the nutritional state of the subject with respect to vitamin C.

Urines were collected in dark-coloured Winchester bottles [which have a capacity of about 2.27 l.] containing 70 g. metaphosphoric acid and the ascorbic acid and dehydro-ascorbic acid contents were determined in the usual way. A standard dose of 700 mg. of ascorbic acid per 140 pounds [about 64 kg.] body-weight was given orally each day. The dose was administered in 50 mg. tablets, as nearly as possible in two equal portions, one at the commencement of each 24-hour collection of urine, the other approximately 12 hours later. This was done in order to minimise the effect of the renal overflow. Blood samples were taken, either at the end of the 24-hour period before the first dose of the subsequent 24 hours, or, if no dose was given, 3 hours after taking food. The plasma ascorbic-acid concentration was determined by direct visual titration of a protein-free filtrate with 2:6 dichlorophenolindophenol.

The behaviour of the plasma ascorbic acid during an extended saturation of the subject with ascorbic acid was observed in nine subjects. Whilst very marked fluctuations

occurred in the urinary excretions, the plasma ascorbic-acid concentrations remained constant. Moreover, if in the same subject the urinary saturation test was repeated, it was found that when the plasma ascorbic-acid content was low, the rise in the daily excretion of ascorbic acid was relatively slow, and no point of sharp demarcation was obvious. If the plasma ascorbic-acid concentration initially was above 0.2 mg. per 100 ml. a spectacular rise in the urinary excretion of ascorbic acid was readily observed and the day on which "saturation" was reached was easily interpreted. Because saturation was attained in some of their subjects who excreted less than 50 % of the test dose during 24 hours, the authors have arbitrarily defined "'saturation'" as the excretion of 33½ % of the test dose based on 700 mg. per 140 pounds body-weight and administered as outlined above."

A figure (III) in this paper shows the relationship between the plasma ascorbic-acid concentration before the saturation test and the dose of ascorbic acid required to bring the subject to a "state of saturation" (18 subjects). At the "state of saturation," the administration of the test dose of 700 mg. per 140 pounds body-weight would result in an excretion of ⅓ of the test dose in the urine in the next 24 hours. The plasma concentration at the "state of saturation" is 0.80 mg. ascorbic acid per 100 ml. The relationship between the two variables is not linear, which may account for some of the divergence of opinion as to the validity of the plasma ascorbic-acid content as an index of vitamin-C nutrition. The maximum charge in the dosage of vitamin C required to produce "a state of saturation" at a given plasma level occurs at a value slightly less than 0.4 mg. per 100 ml. If the initial plasma ascorbic-acid concentration is 0.4 mg. per 100 ml., 450 mg. of ascorbic acid per 140 pounds body-weight will bring the subject to a "state of saturation" which is demonstrated by the further ingestion of 700 mg. on the succeeding day. This is equivalent to a good saturation-response in two days with Harris's urinary saturation test (Harris, 1943).

During the progress of this work 8 subjects were kept for varying periods on controlled intakes of ascorbic acid for known periods. It was found that if the subject has previously been on a higher intake of ascorbic acid and reverts to a lower intake, the plasma ascorbic-acid concentration tends to remain at a higher level than that reached when the procedure is reversed, unless a considerable period on the lower intake is maintained (probably at least 30 days).

The authors conclude that the plasma ascorbic-acid concentration is in man an index of the nutritional state with respect to vitamin C, unless, within the previous 30 days, the subject has been on an appreciably higher intake of ascorbic acid than he is receiving at the time of the test. A level of 0.8 mg./100 ml. represents a "state of saturation" and evidence is presented for the desirability of a plasma ascorbic-acid concentration of not less than 0.4 mg. per 100 ml., for which an intake of approximately 60 mg./day is necessary.

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¹ Harris, L. J. (1943) *Lancet*, 1, 515

² [see *BMB* 107]

504

VITAMIN-C NUTRITION IN A HOSPITAL: With Observations on a Case of Scurvy

by F. T. G. Prunty & C. C. N. Vass, *Lancet*, 1, 180-182, 5/2/44

The concentration of ascorbic acid in the plasma of hospital in-patients and members of the medical and nursing staffs was determined at various times over a year. Seventeen patients taken at random were examined in the period May to July 1942, and fifteen during September and October. In the first period only 6 % would give a saturation response in 2 days to the normal urinary saturation test; the plasma ascorbic-acid concentration averaged 0.12 mg. per 100 ml. with a range of 0.00 to 0.30. In the second period, 27 % of the subjects would have given a positive urinary saturation response in 2 days, as indicated by an average plasma ascorbic-acid concentration of 0.24 mg. per 100 ml. with a range of 0.03 to 0.65. Comparison of the plasma values of the male members of the medical staff showed the same seasonal variation and emphasized the poorer nutrition of the hospital in contrast with the uniformly higher figures found among the non-resident staff. A small group of nurses examined in

February 1943 supplied further evidence of the relative poverty of the hospital diet in regard to vitamin C, whilst a corresponding group of student nurses who resided in a hostel had satisfactory plasma ascorbic-acid levels.

The latter half of the paper contains the results of an extended ascorbic-acid saturation test on a scorbutic mechanic aged 27 years, weighing 131 pounds [about 60 kg.]. He was admitted to hospital on 30/5/42 complaining of rash on his shins for one month, painful swelling of the left forearm and leg for one week, and swelling of the legs for two days. He had a hæmatemesis 2 years previously, afterwards reverting to a normal diet; six months ago there was a sudden onset of gastric ulceration demonstrated radiologically. Since the ulcer had developed he had kept strictly to a diet of two pints [about 1·14 l.] of pasteurized milk, porridge, fish, dry toast, butter and chocolate daily. At examination his gums were edentulous, the soft palate reddened and slightly œdematous. The anterior aspects of both legs were covered with small petechiæ. Œdema of both ankles was marked and the left calf was somewhat swollen and tender. Ecchymoses were present on the inner sides of both ankles, in the right antecubital fossa and on the palmar aspect of the right wrist. The left arm had a fixed flexion of 160° with some tender swelling deep to the extensors of the left forearm. Hyperkeratotic papules were present on the outer sides of both thighs, across the lumbar region and over the dorsal surfaces of both upper arms. A blood count showed 4,390,000 erythrocytes, hæmoglobin 70 % (Haldane), 5,830 leucocytes with a normal differential count and 280,000 platelets. After three minutes at 100 mm. Hg pressure, 30 petechiæ were produced in an area approximately 6 cm. in diameter in the left antecubital fossa.

After daily treatment with 750 mg. ascorbic acid in doses of 400 and 350 mg. at 12-hour intervals, the hyperkeratotic papules disappeared within 7 days and the petechiæ and ecchymoses had largely faded. After 18 days the capillary fragility test gave only 3 petechiæ. A prolonged saturation test was carried out on this subject and plasma ascorbic-acid concentrations were determined at intervals. The results attained were similar to those obtained in non-scorbutic subjects, whose initial plasma ascorbic-acid concentration was also 0·00 mg. per 100 ml. The scorbutic patient was saturated with a total dose of 4,300 mg. per 140 pounds [about 64 kg.] body-weight in 6 days.

Prunty & Vass (1943) have reported a patient with a gastric ulcer and an initial plasma ascorbic-acid concentration of 0·00 mg. per 100 ml. who was saturated in 8 days with a total dose of 4,900 mg. of ascorbic acid per 140 pounds body-weight, and this emphasizes the impossibility of diagnosing scurvy either by determination of the plasma ascorbic-acid by the urinary saturation tests alone. Further, the failure to observe signs of sub-clinical scurvy in this survey substantiates the view that a sub-standard intake of vitamin C is not necessarily equivalent to a clinical deficiency (Harris, 1943).

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² Prunty, F. T. G. & Vass, C. C. N. (1943) *Biochem. J.* 37, 623
¹ [see *BMB* 107] ² [see *BMB* 503]

505

SCURVY: A SURVEY OF FIFTY-THREE CASES

by R. B. McMillan & J. C. Inglis, *British Medical Journal*, 2, 233-236, 19/8/44

This is a report by the medical superintendent and the late senior medical officer of cases of scurvy admitted to the medical wards of the *Eastern General Hospital*, Edinburgh, between August 1937 and February 1944. The patients were 48 males and 5 females whose ages ranged from 41 to 82 years. They formed 0·16 % of the total medical admissions in 1937-38, an incidence which gradually rose to a maximum of 3·07 % in 1941-42 and fell to zero in 1943-44, although the total number of medical admissions, which had fallen to one-third of the 1937-38 total in 1940-41, had almost reached the pre-war level in 1943-44.

Eighty-one per cent. of the patients were aged 65 or over, and 96 % lived alone. More than 90 % cooked for themselves. An analysis of their social and economic background showed that poverty was by no means the whole reason for

the condition. The disease developed most commonly in June, then came May, March and April in that order. In 80 % of cases the time elapsing between the first sign or symptom and admission to hospital was less than one month. The disease, by the usual standards, was mild in 2 instances and moderate in 51; all had skin petechiæ. Where teeth existed, spongy and infected gums were prevalent. The disease appeared first in one leg, then the other, and finally in the arms. Hyperkeratosis perifollicularis was very common but not universal. Three instances each of multiple neuritis and pellagra were also recognized clinically. Neither the positive-pressure cuff test of Hess (1920) nor of Göthlin (Falk, Gedda & Göthlin, 1932) were diagnostic or in alignment with the plasma ascorbic-acid concentration or the saturation requirements.

The vitamin-C content of the urine varied from 1·5 mg. to 16·0 mg., with an average of 7 mg. per 24 hours. Thirty subjects required between 2·0 to 5·9 g. (average 3·85 g.) of ascorbic acid to produce saturation. No steady relationship between the saturation requirements and the clinical extent of the disease was observed. The plasma ascorbic-acid concentration in 22 patients, within 48 hours of admission, varied from 0·00 to 0·29 mg. per 100 ml. There was a constant relation of plasma level to saturation requirements but not to the clinical picture.

A complete blood examination was made on 38 males and 2 females within 48 hours of admission. The hæmoglobin concentration varied from 5·3 to 11·9 g. per 100 ml. An examination of the sternal marrow was made on 6 subjects: 5 were normoblastic, two of these had a few megaloblasts, one was megaloblastic. No constant relationship was noted between the anæmia and the extent of the hæmorrhages, or the plasma ascorbic-acid level, or the saturation requirements of the patients. The anæmia was predominantly normocytic, rarely hypochromic microcytic, and more rarely macrocytic.

Groups of patients were placed on diets containing known quantities of iron with no vitamin C, or with 15 mg. vitamin C, or with a maintenance dose of 100 mg. vitamin C daily after saturation had been attained. The experimental periods lasted from 9 to 25 days. No patient on a vitamin-C-free diet showed a fall in either the erythrocyte count or hæmoglobin, but in most individuals the presence of the vitamin accelerated regeneration.

The authors ascribe three root causes to the production of this "bachelor" scurvy. (i) Ignorance, especially among males, of the need for potatoes and vegetables in the diet. (ii) Apathy, producing absence of the same items because they required preparation and cooking. (iii) Poverty, which made it impossible to buy an adequate diet or to obtain lodgings with adequate cooking facilities.

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Water Metabolism

506

EFFECTS OF DRINKING SMALL QUANTITIES OF SEA-WATER

by W. S. S. Ladell, *Lancet*, 2, 441-444, 9/10/43

The work described in this paper was part of a study of the physiology of persons receiving the same rations as shipwrecked personnel. It was performed on behalf of the committee on the care of shipwrecked personnel of the *Medical Research Council*. The subjects were given the very limited diet which was at that time issued to lifeboats, and consisted of 30 g. of biscuits, 30 g. of sweetened condensed milk, 30 g. of butter or margarine and 30 g. of chocolate per day. This food did not supply the men with enough calories to meet their physical needs and it provided less than 1 g. of salt daily.

Four experiments were carried out, the object of all of them being to study how men reacted when they were given (a) no water, (b) a limited amount of fresh water, or (c) sea-water.

180 cm.³ of sea-water were usually given each day, but up to 400 cm.³ were administered to one person. In all some 25 subjects seem to have been studied. It was found that when the men were getting too little water to satisfy their needs, but were not taking sea-water, they continued to pass 350 to 450 cm.³ of urine per day, and that the volume passed was not related to the severity or duration of the dehydration. The concentration of urea in the urine was high and values up to 6% were found. The urine contained much salt on the first day of water deprivation—which was to be expected as the subjects had until then been taking normal quantities of salt—but thereafter the losses of salt became very much lower.

A diuresis occurred in all experiments in which the subjects drank sea-water, and the excretion of salt remained high or rose if it had been low. The output of water did not rise (on average) by more than the amount of sea-water ingested. There was some evidence that the end-products of N metabolism were more freely excreted when the urine volumes were raised by the sea-water, and the author concludes that these quantities of sea-water diminished or prevented N retention.

The author considers that, in addition to these physiological effects, there was a definite psychological value in having additional fluid to drink even if it was salt to the taste. However, in a footnote to this paper, Dr. B. S. Platt of the *Medical Research Council* points out that, taking into consideration other relevant evidence, the drinking of sea-water was *not* recommended.

507

A STUDY OF DEHYDRATION BY MEANS OF BALANCE EXPERIMENTS

by D. A. K. Black, R. A. McCance & W. F. Young, *Journal of Physiology*, 102, 406–414, April 1944

The work described in this paper was carried out at the Department of Medicine, Cambridge, to study man's reactions to a deficiency of water. Two men, one of them an author of the paper, drank no fluids for three and four days respectively, and maintained their normal calorie intake by eating food containing very little water, such as biscuits, butter, jam, cheese and bread.

On this régime the men lost weight, and by the third or fourth day it became very difficult indeed to swallow the dry food. Their voices changed slightly, their faces became rather sunken and pale, and their lips cyanosed. It was evident that their efficiency was impaired. These changes were observed in other subjects and are considered to be characteristic of water deprivation. This general appearance of ill-being vanished within a few hours of the restoration of fluid.

Changes in the circulating fluids were investigated, and determinations of nitrogen and mineral balance were carried out on these two men. It was found that in spite of a loss of weight which amounted to nearly 4 kg.—most of which was water—there was practically no rise in the plasma proteins, or in the haematocrit. It was evident that the volume of the blood had been maintained at the expense of the fluid in some other compartment of the body. The sodium in the serum rose by about 10% and the potassium fell. The urea was raised to double its normal level. Dehydration led to an increased production of urea within the body, and it is suggested that this was due to a breakdown of tissue protein. The output of nitrogen fell on the first day of dehydration, due to the fall in the volume of urine, but rose on subsequent days as the level of urea in the blood increased. The men lost about 3,500 cm.³ of their body water and it is estimated that about $\frac{1}{3}$ of this came from the extracellular fluids, the remainder from the fluid within the cells.

Although both subjects excreted about as much sodium as their food contained, they excreted none of the sodium corresponding to the extracellular fluids which they lost. In spite of the fall in the serum potassium, the men excreted rather more potassium than they took in with their food, but again, not enough to prevent a rise of potassium in their cellular fluids. Consequently the osmotic pressure of the whole body rose, and, in the light of some experiments which were carried out by Kerpel-Fronius & Leövey in 1929 and 1931, the authors consider that a retention of osmotically-active substances within the body must be seriously

considered as the ultimate cause of death in prolonged dehydration.

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508

THE SECRETION OF URINE DURING DEHYDRATION AND REHYDRATION

by R. A. McCance & W. F. Young, *Journal of Physiology*, 102, 415–428, April 1944

This paper deals with the reactions of the kidney to a shortage of water within the body, and the work was done in conjunction with that reported by Black, McCance & Young (1944). Twelve persons were dehydrated, ten men and two women, and the method used was similar to that described by Black *et al.* It was first shown by experiments on four people that dehydration, sufficiently prolonged to make the subjects lose 4–7% of their body-weights, made little difference to the inulin and diodone clearances, i.e. to the glomerular filtration-rates and to the effective blood flow through the kidney. Hence the urinary changes which characterize dehydration of this degree of severity must be essentially the results of changes in tubular activity.

The authors next tried the effect of giving large doses of urea and of sodium and potassium chloride to persons who had been deprived of water for some days. These substances were given as hypertonic solutions. One person took 500 cm.³ of 3.6% sodium chloride by mouth, and another was given 350 cm.³ of 10% urea intravenously. The effects produced in the dehydrated subjects were not unlike those produced in the same persons when they were normally hydrated. The flow of urine was increased, and the diuresis produced by sodium and potassium chlorides raised the urea clearances. The osmotic pressure of the urine fell somewhat as the volume rose, and the osmotic pressure of the body must have been increased. One interesting effect followed the administration of the urea during dehydration. The serum chloride fell from 391 to 359 mg. per 100 cm.³ and there was a profound fall in the excretion of this ion.

Balance experiments were also carried out, and it was shown that the volume of the urine passed during the days of dehydration depended largely upon the quantity of salt in the food. The volumes of urine, however, passed on the second, third and fourth days of water deprivation were no smaller than those passed on the first day. In diets containing some 12–15 g. of salt, the output of water by the kidney ranged from 633 to 815 cm.³ in the 24 hours. When the salt intake was reduced to 2–5 g. per day, the daily urine output fell to 365–413 cm.³ As the high salt diets contained no more water than the low salt diets, the additional water excreted must have come from the already depleted body-water, and it is evident that a diet containing very little salt would enable persons on a reduced water intake to conserve 300 to 400 cm.³ of their precious store of body-water every day.

When persons, who had been deprived of water for some days, and who had been taking 5–15 g. of salt, were rehydrated in stages, the urine volumes fell, the percentage of chlorides in the urine fell, and the percentage of urea rose. Thus one subject, who had been passing 605 cm.³ of urine per day on a water intake of 470 cm.³, reduced his urine volume to 506 cm.³ when he was given 3804 cm.³ of water in 24 hours. This paradoxical finding was explained thus: With the onset of rehydration, the concentration of chlorides in the body-fluids fell and there may have been some alteration in the activity of the adrenal cortex. Following these changes, so much less salt presented itself for excretion that (a) the kidneys were able to reduce the output of the urine, (b) as the concentration of chlorides in the urine also fell, the kidneys were able to raise the concentration of urea in the urine without raising the osmotic pressure.

These experiments confirm that shipwrecked mariners should not drink sea water and cannot possibly do themselves any good by drinking their own urine.

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- ¹ Black, D. A. K., McCance, R. A. & Young, W. F. (1944) *J. Physiol.* 102, 406
¹ [see *BMB* 507]

DISCUSSION ON WATER METABOLISM IN SICK AND HEALTHY INFANTS

by W. F. Young, R. A. McCance, F. Avery Jones & R. Dobbs, *Proceedings of the Royal Society of Medicine*, 36, 219-221, March 1943

Dr. Young pointed out that, because infants frequently suffer from gastro-enteritis, an understanding of their water metabolism, and particularly of the differences in the water metabolism of infants and adults, is of considerable practical importance. A full-term baby contains 75%-80% water, and an adult only 60%-65%. Further, of the total body-water, 65% is extracellular in the infant, but only 28% in the adult. Studies by McCance & Young (1941) have shown that the kidney of the infant at birth is a relatively inefficient organ, and that the infant therefore needs a relatively high intake of water. In premature infants the renal inefficiency is even greater, and the clinically familiar liability of premature infants to become oedematous can be attributed to their low mineral clearances. Glomerular filtration rates are also low as judged by adult standards.

Whenever the output of water by other routes (skin, lungs, bowel) is increased, the infant's urine volume should be maintained by increasing the intake of water. Salt should also be given when there is diarrhoea or vomiting. As the gastro-intestinal secretions may be regarded as isotonic, salt-loss may be replaced by giving an equivalent volume of 0.9% NaCl. However, a hypotonic solution of salt should always be given to an infant with gastro-enteritis, as some water (but not salt) is being excreted by the skin and lungs. In giving fluids by the intravenous route, solutions of (i) 0.9% NaCl and (ii) 5% glucose should be given in varying proportions, according to the estimated requirements.

To enable the body to restore mineral equilibrium, enough water must be given to establish a free flow of urine, but salt requirements should be carefully assessed, whether the oral or a parenteral route is being employed. The rectal route is useful only for supplementing the oral intake when the infant is vomiting but has no diarrhoea. The subcutaneous route should be used only as a supplement to oral feeding, as the solution given is isotonic (0.9%) NaCl. The intravenous route is often the only one by which the body-fluids can be restored sufficiently rapidly. Whatever route is adopted, accurate charting of output is essential, and a daily record of the body-weight is helpful, in assessing requirements. Change in weight is a more sensitive indication of water balance than serum chemistry.

Dr. McCance emphasized the difference between true dehydration (due to deficiency of body-water) and salt deficiency (usually due to loss of water and salt with partial or total replacement of water), and illustrated his point by a description of personal experiments. By making himself salt-deficient he lost not more than 6 pounds [about 2.7 kg.] weight, and there was clear evidence of severe hæmoconcentration, with a serum-sodium below the normal level. When he dehydrated himself, he lost almost 10 pounds [about 4.5 kg.] without difficulty, his serum-sodium rose to abnormal levels, and there was no reduction in blood volume. True dehydration is seldom encountered in temperate climates, and clinically there is usually a loss of salt as well as water (as in vomiting, diarrhoea, diabetic coma, Addison's disease). Patients should be given saline solutions until the body weight has been restored, and it is then better to use 5% glucose solution for intravenous infusion unless salt is still being lost. This provides water for lung- and skin-losses without overburdening the kidneys with salt.

Dr. Jones said that it had been shown that the routine use of normal saline infusions after surgical operations involved a risk of water retention with hydræmia and a tendency to oedema of the lungs or of the intestinal suture line. Many sick infants were given the excessive amount of 12 g. of salt, which was equal to the total salt content of an infant's body.

Dr. Dobbs said that practising pædiatrics were not sufficiently informed on the important physiological changes underlying the clinical conditions of "dehydration," "shock" and "collapse" in infants with acute gastro-enteritis. Discussing different routes of administration, he regarded subcutaneous infusion as the safest. The oral route might be inefficient and the indiscriminate employment of the intravenous route might result in such complications as heart failure and cerebral or pulmonary oedema.

REFERENCE

McCance, R. A. & Young, W. F. (1941) *J. Physiol.* 99, 265

510

THE RENAL FUNCTION OF NEWBORN INFANTS

by H. Heller, *Journal of Physiology*, 102, 429-440, April 1944

Dr. Heller has worked for a number of years on the comparative physiology of the anti-diuretic principle of the pituitary gland and the investigation reported in this paper follows the work of McCance & Young (1941) on urinary excretion in infancy. The present author has studied the effect of this hormone upon the new-born infant. The action of posterior pituitary extracts on adults is too well known to require description, and small doses have been used for many years in the treatment of diabetes insipidus. Their action is always to reduce the flow of urine even after copious draughts of water. Dr. Heller administered injections of an extract of posterior pituitary gland to infants and studied the effect upon the concentration of the urine and the depression of its freezing point. A dose of 125 milli-units per metre² of body surface produced a striking effect upon an adult, but a negligible effect upon an infant 5 days old, and raising the dose to 250 milli-units per metre² had little more effect. The author concludes that at birth, and for some time after it, the renal tubules of newborn children are relatively insensitive to the action of the posterior pituitary principle. This is an interesting contribution to the physiology of infancy.

Dr. Heller goes on to show that infants with a reduced intake of water can produce a urine more concentrated than the blood, so that they are not quite in the position of the patient with diabetes insipidus. Nevertheless, even these urines are much less concentrated than those normally passed during adult life, and it is evident that infants must have an abundant supply of water if they are to maintain their normal renal function.

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McCance, R. A. & Young, W. F. (1941) *J. Physiol.* 99, 265

Mineral Metabolism *

511

SEASONAL AND ANNUAL CHANGES IN THE CALCIUM METABOLISM OF MAN

by R. A. McCance & E. M. Widdowson, *Journal of Physiology*, 102, 42-49, June 1943

The authors, writing from the Department of Medicine of the University of Cambridge, point out that the capacity of an individual to absorb calcium has been known to vary for a number of reasons. It is believed to be increased during the waves of growth in children; and as rickets, tetany and osteomalacia have been noted to be at their worst in late spring, responsibility has been attributed to the decreased amount of vitamin D formed in the skin in the winter months, because of the effect of vitamin D on calcium absorption.

During experiments on the effect of brown bread on calcium absorption, it was found that the subjects (three human beings for the whole period, five others for a portion of the time) absorbed calcium less freely in November than they did in July. By the following March, in three of the subjects who were still carrying on the experiment, it was clear that the Ca metabolism had changed very much since they had first come under observation.

Experimental methods: The method of estimating absorption of Ca has been described by the authors elsewhere (McCance & Widdowson, 1942a, 1942b). The amount of flour used in the diet (either white or brown) always contributed 40%-50% of each person's calories, the rest of the diet was freely chosen but was very similar from one experiment to the next. Most of the figures in the present paper are based on the results of 3-week experiments; some are based on 2-week experiments and a very few on those which lasted only 8 days.

Results: In one man and two women, well defined seasonal changes in calcium absorption were observed. The subjects

* [see also *BMB* 521, 526, 536]

were under observation for two summers and three winters. They absorbed Ca much more freely in July and August than they did in February and March. This seasonal effect was apparent irrespective of whether white or brown bread was eaten, but the figures were always lower on the latter. The magnesium absorptions were not affected by the seasons and showed a constancy from one season to another which was quite remarkable. It was also found that the three subjects absorbed Ca better in the summers of 1940 and 1942 than they did in 1941. Again there was no variation in the Mg absorption and no seasonal or annual change in the absorption of phosphorus could be observed.

At first it was thought that these changes in absorption were due to changes in the amount of vitamin D in the food or in the amount formed by the sun in the skin. However, the administration of 2,000 international units of vitamin D per day for seven preliminary and 21 experimental days, resulted in negligible increases in the calcium absorption. These fluctuations in Ca absorption appear to be due to some factor or factors in Ca metabolism hitherto undescribed, and the authors suggest that they may be due to variable resistance of the tissues of the body to the action of vitamin D.

From a purely practical point of view it should be noted that all those investigating Ca metabolism over a period of months should be aware of the possibility of having their results vitiated by these variable absorptions.

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- ¹ [see BMB 15]

512

THE EFFECT OF NATIONAL WHEATMEAL ON THE ABSORPTION OF CALCIUM

by H. A. Krebs & K. Mellanby, *Biochemical Journal*, 37, 466-468, 1943

This report from the Department of Biochemistry in the University of Sheffield and the Sorby Research Institute, Sheffield, is a continuation of the work of McCance & Widdowson (1942), but more particularly in regard to the *National Wheatmeal* flour of 85 % extraction which has been introduced by the Ministry of Food. Six male volunteers whose ages were between 23 and 31 years were kept on a diet yielding 4100 calories per diem, which included at least 500 g. flour (dry weight) and not more than an average of 0.55 g. calcium per diem. Of the flour, an average of 70 g. (dry weight) was taken in the form of cooked dishes, the remainder as bread. After preliminary trials the main experiment consisted of two periods. During the first, lasting four weeks August-September 1941, *National Wheatmeal* flour (85 % extraction) was used. The second period of four weeks September-November (1941) was the control period, when "white" flour (75 % extraction) was used. The phytic-acid phosphorus content of the *National Wheatmeal* flour was 140 mg. per 100 g. and of the bread 41.4 mg. per 100 g.

Under the experimental conditions outlined above, the consumption of *National Wheatmeal* flour was accompanied by an average calcium loss of 0.110 g. per diem. When this flour was replaced by 75 % extraction flour, the average loss was 0.023 g. per diem. The effect of the *National Wheatmeal* flour was definite in every individual case. In a preliminary experiment where the average intake of *National Wheatmeal* bread was about one pound [about 0.45 kg.] per diem (instead of 1.7 pounds) and the average daily calcium supply 0.94 g., the calcium balance was in equilibrium.

REFERENCE

- ¹ McCance, R. A. & Widdowson, E. M. (1942) *J. Physiol.* 101, 44
- ¹ [see BMB 15]

513

THE RELATIVE EFFICACY OF CALCIUM CARBONATE AND CALCIUM PHOSPHATE IN PREVENTING RICKETS IN RATS

by J. Yudkin, *Biochemical Journal*, 37, 543-546, 1943

In the absence of vitamin D, calcification of bone is to a large extent dependent on the Ca/P ratio in the diet. With the

proposal to add calcium carbonate to *National Wheatmeal* flour, the author, who holds a Sir Halley Stewart Research Fellowship at the Dunn Nutritional Laboratory of the University of Cambridge, has compared the power of the carbonate and the phosphate to prevent rickets in rats.

Young rats weighing about 50 g. and kept in separate cages were placed on diets of 85 % extraction flour plus 1 % sodium chloride to which were added varying amounts of calcium carbonate as *creta preparata* (B.P.) or calcium monohydrogen phosphate (CaHPO_4). As controls, the flour was replaced by a white (75 % extraction) flour, plus daily supplements of aneurin and riboflavin, or a diet containing 76 parts maize meal and 20 parts gluten. The highest amount of each salt added to the diet was equivalent to 3 % of calcium. After five weeks on these diets, the ash content of both femurs of each animal was determined and the knee-joints of the rats were x-rayed.

Using white (70 % extraction) flour and no added calcium, the ash content was between 32 % and 35 %. On adding calcium phosphate, the maximal ash content of about 50 % was reached with approximately 0.4 % calcium, and increasing the calcium to 3 % had little effect. With the carbonate, a maximum ash content of 42 % was reached with 0.2 % calcium. Increasing the calcium carbonate reduced the ash content until at a level of 3 % calcium intake the ash content was only 28 %. Similar results were obtained when *National Wheatmeal* (85 % extraction) flour was used, except that the maximal ash content reached with approximately 0.2 % calcium administered as carbonate was the same as that when phosphate was fed. Similar results were obtained in experiments with maize-gluten diet. The rate of growth on the flour diets was less with the carbonate than with the phosphate; this was reversed on the maize-gluten diet.

The Ca/P ratio in white flour is 0.16, in *National Wheatmeal* flour 0.10, and in maize-gluten 0.10. Addition of calcium hydrogen phosphate (with 1.2 % calcium as phosphate) increases the ratio to approximately 1.0 for all diets. Addition of calcium carbonate increases the ratio to much higher levels; 0.2 % calcium as carbonate gives a ratio of 2.05 for white flour, 1.10 for *National Wheatmeal* flour and maize-gluten. At higher levels of carbonate a rapid rise in the ratio occurs; at 1.2 % Ca the ratio is between 5 and 10 and at 3 % Ca between 13 and 28. Thus maximum calcification recurred in all instances with Ca/P ratio between 1 and 2.

514

EXPERIMENTS ON THE PRACTICABILITY OF INCREASING CALCIUM ABSORPTION WITH PROTEIN DERIVATIVES

by T. C. Hall & H. Lehmann, *Biochemical Journal*, 38, 117-119, 1944

McCance, Widdowson & Lehmann (1942) showed that by increasing the "protein" intake from about 60 to 160 g. protein per diem, the calcium absorption was increased. The present authors have examined the urinary excretion of calcium following the ingestion with peptone or with lactose. They have devised a powder containing 100 mg. calcium hydrogen phosphate (CaHPO_4), 2,000 mg. peptone, 200 mg. glutamic acid, 550 mg. lactose and 150 mg. gum acacia. A powder in which lactose replaced peptone and glutamic acid was used as a control.

After 14 hours, during which food and water were withheld, 12 control powders were given with 750 ml. water. The urine was collected during the next 5 hours and its calcium content was determined after conversion to ash. After an interval of at least 3 days, but not more than 5 days, 12 "peptone" powders were given and the procedure was repeated.

Nineteen experiments were carried out on 18 inmates of a mental hospital. In 14 subjects the urinary calcium was higher after the "peptone" powders than after the "control" powders. Even when the amount of peptone was halved, a rise in the urinary calcium was still evident. In agreement with the work of McCance & Widdowson (1939), where a normal serum-calcium existed before the test, the ingestion of the "peptone" powders did not raise the serum-calcium level. In one subject, however, with an initial serum-calcium of 0.8 mg. per 100 ml., the serum-calcium rose to the normal level on the "peptone" powder but not on the "half-peptone" or lactose powders. After withdrawal of the

"peptone" powder, the serum-calcium declined to its initial level in 3 weeks.

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¹ [see *BMB* 99]

515

PHYTIC ACID AND IRON ABSORPTION

by R. A. McCance, C. N. Edgcombe & E. M. Widdowson, *Lancet*, 2, 126-128, 31/7/43

An element must presumably be in solution if it is to be absorbed, and the presence in the diet of a radicle which precipitates the element will depress absorption. It has been shown by McCance & Widdowson (1942 a, b) that phytates depress calcium absorption. Barrett (1942) has shown that calcium depresses oxalate absorption by the formation in the intestine of the relatively insoluble calcium oxalate. In experiments on the effect of brown bread on absorption of calcium, Widdowson & McCance (1942) found some evidence that the phytic acid in brown bread might interfere with the absorption of iron.

Four normal men and 5 normal women were used for the present experiments. Each person carried out 4 tests, 2 to measure the effect of sodium phytate on the absorption of ferrous iron and 2 to make a similar study with ferric iron. In some cases additional experiments were carried out in which phosphates replaced phytates. After an overnight fast the subject came to the laboratory and a sample of blood was taken. Breakfast consisted of bread and jam and ferrous or ferric ammonium sulphate. The amounts eaten by each individual were equal to 1.8 g. bread, 1.1 g. jam and 8 mg. iron per kg. body weight. The iron salt was mixed with jam and spread on the bread. Sodium phytate was incorporated into the diet when desired by mixing it with the bread dough (made from low-extraction flour) before baking. When the effect of phosphate was being studied, di-sodium hydrogen phosphate was added to the bread in similar proportion. Samples of blood (from the antecubital vein, using stainless steel needles) were collected 1½-2 hours, 4-5 hours, and 7-8 hours after breakfast. In the estimations, the iron of the serum was converted to ferric thiocyanate, and the intensity of the colour developed was compared with that of a standard in a photo-electric colorimeter. It was found that sodium phytate interfered with the absorption of iron. Disodium hydrogen phosphate had a similar but less regular effect. The absorptions of both ferrous and ferric iron were affected by sodium phytate, but there was a greater retarding effect on the absorption of the latter.

Without the sodium phytate it was found that appreciable quantities of iron were absorbed from the intestine after a large dose of soluble iron salt. If sodium phytate added to bread has such an effect, it is fairly certain that the phytates of whole cereals would behave similarly and would be capable of immobilizing iron present in the rest of the diet.

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¹ [see *BMB* 194] ² [see *BMB* 15] ³ [see *BMB* 14]

Vitamin-B Complex* : Nitrogen

516

STUDIES IN VITAMIN B DEFICIENCY WITH SPECIAL REFERENCE TO MENTAL AND ORAL MANIFESTATIONS

by A. G. Clarke & F. Prescott, *British Medical Journal*, 2, 503-505, 23/10/43

This report from the *West End Hospital for Nervous Diseases* and the *Wellcome Research Institute*, London, deals with 17

* [see also *BMB* 493, 494, 495, 496, 520, 522, 523, 524, 533, 534, 536, 537, 539, 543]

cases of deficiency of the vitamin-B complex in patients who were being treated primarily for functional nervous disorders, the main symptoms of which were depression, headache, insomnia, and loss of appetite. Other symptoms were lack of energy, fatigue on slight exertion, breathlessness, inability to concentrate, and nervous dyspepsia. There was one case of psychosis and four patients had peripheral neuritis. All the patients had glossitis and nearly all cheilosis. Seven typical case records are given in the original paper, which also contains photographs illustrating the effect of treatment. Although in most cases the deficiency seems to have been determined by the wartime diet, it was actually precipitated only when mental or physical factors led to loss of appetite or impaired absorption. These factors included adherence to special diets (for peptic ulcer, obesity, and hypertension) and conditions interfering with the absorption of food (vomiting and gastro-intestinal diseases).

Striking improvement occurred in all the cases as the result of treatment with vitamins of the B complex without alteration of the environment or special psychological measures.

517

SOME PROBLEMS IN RIBOFLAVIN AND ALLIED DEFICIENCIES

by H. S. Stannus, *British Medical Journal*, 2, 103-105 & 140-144, 22/7/44 & 29/7/44

These two papers are the substance of the Lumleian Lectures delivered before the *Royal College of Physicians* of London in April 1944. During the years 1912 to 1913, the author published an account of an outbreak of pellagra amongst long-term prisoners in Nyasaland whose staple diet was rice. Attention was directed to a group of symptoms which tended to precede the onset of the classical signs of pellagra by some months, and in some instances persisted without the development of frank pellagra. The manifestations included: soreness of tongue and lips with a characteristic lesion at the corners of the mouth, and with a similar condition about the nostrils, palpebral fissures, the free border of the prepuce, the vulva and anus, together with a dermatosis of the scrotum, often also involving the skin of the adjacent part of the thigh. This syndrome, limited to lesions of the oral aperture, was not uncommon among the general native population. Amongst the prison patients, deafness and dimness of vision were also noted but not associated at that time with the syndrome.

In 1936, the author collated a number of published observations which he considered were akin to the original syndrome and used the term "pellagra-like conditions" in order to focus attention upon malnutrition as the cause. Moore (1930-1937) and Landor & Pallister (1935) published accounts in which the original syndrome was described and attributed to a dietetic deficiency which responded to autoclaved yeast or marmite.

In 1938, Sebrell & Butler extended the animal experiments of Goldberger & Tanner (1925) to include man. Eighteen women were kept on a riboflavin-free diet, and after 94 to 130 days, 10 of them developed lesions on the lips, at the angles of the mouth, in the vestibule of the nose, etc., comparable to those described by Goldberger & Tanner as "pellagra sine pellagra" in their animals and those described by Stannus in man. As these lesions disappeared after riboflavin therapy they suggested that "the term ariboflavinosis be added to the nomenclature of the vitamin-deficiency diseases as a designation for the clinical condition due to riboflavin deficiency." Stannus prefers the term "hypo-riboflavinosis", as there is reason to believe that death occurs long before the advent of ariboflavinosis. Later work has extended the symptoms and signs of ariboflavinosis (see Sydenstricker, 1941), but the present author holds that the differences between the newer syndrome of ariboflavinosis and those included in the older syndrome are differences in degree only. Many groups of symptoms, combined into a series of overlapping syndromes due to malnutrition during the Spanish Civil War 1936-9 have been described by Márquez Blasco & Peraita (1940), Jiménez García & Grande Covián (1940).

As riboflavin forms the link between the anaerobic dehydrogenase system and the aerobic cytochrome: cytochrome-oxidase: oxygen system, Stannus suggests that in

hyporiboflavinosis the capillary endothelium will be one of the first tissues to suffer from the induced anoxia. This anoxia produces a derangement of function which he terms "capillary dysergia", with the development of loss of tone, dilatation and a decreased rate of flow of the blood, which in turn leads to a disturbance of the internal environment and so to a metabolic disorder of the adjacent tissues. If this is so, the signs of hyporiboflavinosis will be first manifested in those tissues with a high metabolic activity and a marked degree of capillarity. On this hypothesis the author offers an explanation of the nature and distribution of the signs and symptoms of a riboflavin deficiency. The worsening of the hyporiboflavinosis lesions as a result of the administration of nicotinic acid is attributed to the vasodilator action of that substance. Of the ocular manifestations, Stannus holds that dimness of vision, which has to a large extent been disregarded by American observers, is part of the general capillary dysergia which produces a condition akin to a retrobulbar optic neuropathy. As to the question of corneal vascularization, he deplors the fact that few workers in this field appear to be cognisant of the work of Graves (1934) on the vascularization of the cornea and believes that the vascular changes can be successfully studied only with the aid of capillario-dilator and -constrictor drugs. The author does not believe that it is possible to formulate any satisfactory notation for describing the degree of vascularity of the limbus and cornea, as has been attempted by Lyle, Macrae & Gardiner (1944). From his observations by slit-lamp microscopy of the eyes of nearly 5,000 subjects, between 3 and 93 years of age, Stannus believes that there is always a complete limbic plexus and that there is no narrow avascular zone between the limbic plexus and the sclero-corneal junction. Whilst corneal vascularization is not an unequivocal sign of hyporiboflavinosis, it does occur.

Following the work of Philpot & Pirie (1943), who suggested that the corneal supply of riboflavin might be through the lacrimal secretions rather than the blood of the limbal loops, Stannus believes that the earliest trophic changes in the cornea, due to riboflavin deficiency following a decreased lacrimal secretion, produce proliferation-promoting intercellular hormones (Loofbourow, 1942; Loofbourow, Webb, Loofbourow & Abramowitz, 1942) which stimulate the loops of the limbic plexus to throw out new vessels. This would also afford an explanation of the similar if not identical corneal vascularization met with in vitamin-A-deficient rats (Wolbach & Howe, 1925). The neurological symptoms included in the syndrome under discussion, all of which are sensory and comprise muscle weakness, inco-ordination, ataxia, paræsthesia and loss of visual and auditory acuity, are considered to arise from disturbances of the capillary supply, particularly to synaptic structures in the cerebellum, and are in accord with the degree of capillarity of the various parts of the nervous system as determined by Craigie (1940). The author believes that the little pathological evidence which is available concerning hyporiboflavinosis supports his viewpoint.

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 [see BMB 523]

THE NUTRITIVE VALUE OF THE NITROGENOUS SUBSTANCES IN THE POTATO AS MEASURED BY THEIR CAPACITY TO SUPPORT GROWTH IN YOUNG RATS

by H. Chick & M. E. M. Cutting, *Lancet*, 2, 667-669, 27/11/43

This paper from the Nutrition Division of the Lister Institute was the result of work carried out to test the advisability of substituting potatoes for a proportion of the wheat consumed in Britain, with a view to economy of shipping space. Dried potatoes differ little from flour from a calorific point of view, but, as usually eaten, the potato has a much lower calorie value as it contains 75 % of water, as opposed to 33 % in the case of bread. Potatoes are a better source of vitamins than wheat. They have approximately as much vitamin B₁, riboflavin and nicotinic acid as wheat and, in addition, may contain appreciable amounts of vitamin C. No fat-soluble vitamins are present.

The potato contains about half the amount of nitrogen present in wheat and about $\frac{1}{3}$ to $\frac{1}{4}$ the amount of protein. The potato differs from wheat in having about half its nitrogenous substances in the form of amides, amino-acids and purines. Kon & Klein (1928) have demonstrated that, weight for weight, the nitrogen of the potato is at least as efficient as the nitrogen of wheat for the maintenance of nitrogenous equilibrium in adult man and animals. Unfortunately, however, the large proportion of starch in potatoes suggests that it would be necessary to eat an impossible bulk in order to obtain enough nitrogenous matter for the optimum requirements of growth. The experiments reported in the present paper had the object of comparing the effect of potatoes with wheat on the growth of young rats from the time of weaning.

King Edward potatoes were used, containing 1.8-2.2 % of nitrogen (reckoned on the dry weight). In some experiments the protein separated from the expressed juice was used as a source of nitrogen, in others the protein-free juice was used, and in others the whole potato. Vitamin and mineral supplements were given as well. The intake of dried food for all rats in one group was measured together, as well as the dry weight of the faeces passed and their nitrogen content.

The value of the nitrogenous substances in the potato for supporting growth in young rats was found to be somewhat greater than those of whole wheat. Addition of sodium citrate to the wheat diet in amounts sufficient to make the alkalinity of its ash equal to that of the potato was without effect. A diet containing 9 % of tuberin, the soluble protein of potato juice, was equal to one containing 11 % whole wheat protein, but not equal to one containing 11 % casein.

The results obtained can be explained only by assuming that some portion of the non-protein nitrogenous substances in the potato complements the amino-acids of its protein to produce a mixture of biological value not less than that of protein itself.

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519

THE BIOLOGICAL VALUE OF MIXED PROTEINS IN FOOD SERVED IN ROYAL AIR FORCE AIRMEN'S MESSES

by T. F. Macrae, K. M. Henry & S. K. Kon, *Biochemical Journal*, 37, 225-230, July 1943

Relatively little is known of the biological value of proteins as supplied in mixed human diets. The authors of this paper report experiments to determine the biological value of the combined proteins in food served at 4 Royal Air Force Stations. At each Station the total food available to 5 airmen at all meals during 1 week was collected, stored at -20° C. for 7 days, and pulverized in the frozen state. The pulverized frozen material was dried at a temperature of 70° C., and then minced and finally pulverized in a coffee-mill. The resultant product was a fine brown-coloured powder.

The biological values and 'true digestibilities' of this product as obtained from each of the 4 Stations were determined by the method of Mitchell (Mitchell, 1924; Mitchell & Carman, 1926), using rats. The results of the tests are tabulated in full. They showed that the product obtained from the diets from each of the 4 Stations had high biological

values (from 77.6 to 81.2) and a high degree of digestibility, 'true digestibility' coefficients ranging from 83.5 to 86.3). Of single foodstuffs, only eggs and milk surpassed the mixed proteins of these diets in biological value. In their discussion of results, the authors compare the figures obtained with those from comparable experiments from India and China.

This paper is briefly reported here because of the interest of the method of converting a mixed diet to a homogeneous and stable product of great convenience for experimental purposes. For full details of method and results, reference should be made to the original paper.

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Vitamins and Bone-Growth

520

EFFECT OF VITAMIN B ON THE GROWTH OF FIBROBLASTS

by E. Paterson & M. V. Thompson, *Biochemical Journal*, 37, 501-505, October 1943

The effect on growth of the B-complex vitamins has usually been examined *in vivo* and vitamin B₁ has been assayed by its effect on the growth of laboratory animals. These experiments from the *Southport* Research Laboratories of the *Christie* Hospital and *Holt* Radium Institute, Manchester, were designed to test whether the growth-promoting effect could be demonstrated *in vitro* on explants of fibroblasts from the choroidal and sclerotic layers of the eyes of 9-day chick embryos cultured by the hanging-drop method. Under standard conditions of preparation and culture, growth was assessed at the end of 48 and 96 hours in terms of the increase in area of the culture determined by measuring with a planimeter the area of a projected drawing of the explant. All the results were compared statistically, the degrees of freedom ranging between 33 and 87.

It was found, in the first place, that extracts prepared from brains of pigeons, in which beri-beri had been produced by the method recommended by Kinnersley, Peters & Reader (1928), were growth-promoting to fibroblasts, the effect being proportional to the concentration of the extract. It was then shown that such extracts were significantly less growth-promoting than extracts from normal pigeon brains. Further experiments involving the separate addition of aneurin and an extract of brewer's yeast to growing explants gave rise to the conclusion that some component of the B complex is growth-promoting *in vitro*. This factor is probably not either aneurin or biotin. The addition of aneurin could not be shown to increase growth whether the medium was or was not deficient in its content of the B-complex vitamins.

The methods described in this paper may be satisfactory for further direct testing of the growth-promoting properties of other constituents of the B complex.

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521

SOME EXPERIMENTS ON THE POSSIBLE RELATIONSHIP BETWEEN VITAMIN C AND CALCIFICATION

by G. Bourne, *Journal of Physiology*, 102, 319-328, December 1943

It seems well established that adequate amounts of vitamin C are essential for the laying down of the organic matrix of bone (see, for example, Bourne, 1942a), but the evidence so far available favours the view that the vitamin plays no part in the process of calcification.

The work reported in this paper from the University Laboratory of Physiology, Oxford, seeks to clear up this point. Guinea-pigs, maintained on a scorbutic diet and injected with graded supplements of vitamin C, were fed alizarin Bordeaux

(1:2:5:8 tetrahydroxyanthraquinone), the special property of which is to stain newly-deposited bone salt. The results suggested that the vitamin does play a part in the laying down of bone salt. These experiments, however, did not show how far the better deposition of bone salt in the animals receiving supplements of the vitamin was simply due to greater availability of the necessary matrix.

By a technique previously described (Bourne, 1942b), observations were made on the calcification process in a 1 mm. hole bored aseptically in the femur of each of a number of guinea-pigs receiving ascorbic acid at various levels. By an ingenious device an attempt was made to differentiate the effects of ascorbic acid on developing trabeculae and (if any) on calcification. These experiments were followed by observations on costo-chondral junctions stained variously by von Kossa's silver nitrate method for demonstrating bone salt and by cobalt chloride and ammonium sulphide (Gomori) for freshly deposited calcium phosphate. The results again suggested that vitamin C is associated with the process of calcification, but it was found impossible to separate its functions in respect of bone-matrix formation and calcification since these two processes are simultaneous.

Further investigations supported the results of Shwachman & Gould (1942) that bone phosphatase is reduced in the scorbutic guinea-pig. "It appears likely that one of the functions of vitamin C is to allow the production of a phosphatase-impregnated bone matrix upon which bone salt is immediately deposited. Vitamin C may play some part in the formation or stabilization of alkaline phosphatase."

Neither vitamin P ("citrin" Roche) nor sodium citrate resulted in the formation of more osteoid tissue, or in the deposition of more bone salt, than vitamin C alone.

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¹ [see *BMB* 17]

Ocular Manifestations of Nutritional Deficiency *

522

OCULAR SIGNS OF RIBOFLAVIN DEFICIENCY

by W. J. W. Ferguson, *Lancet*, 1, 431-433, 1/4/44

Since Sydenstricker, Sebrell, Cleckley & Kruse (1940) described certain ocular signs and symptoms which responded to riboflavin therapy, many workers have reported widely conflicting results. The author of this paper, who is the senior ophthalmic surgeon at the *Sheffield Royal Infirmary*, believes that differences have arisen mainly through lack of experience in the use of the slit-lamp, an imperfect understanding of the normal variations of the appearance and vascularity of the limbus, and the inclusion of corneal vascularization due to other causes than riboflavin deficiency; but a particular recognizable type of corneal vascularization which rapidly responds to adequate riboflavin therapy does exist. He deprecates the term "circumcorneal injection," as the limbic plexus becomes congested and engorged on the slightest provocation.

Riboflavin deficiency produces a vascularization which is an extension of the normal limbic vascular system to the true cornea. The vessels are of very small calibre and run superficially immediately under the epithelium, and they are best seen with a corneal microscope and slit-lamp when observed by light reflected from the iris. In reflected light, the vessels appear as very fine cobweb-like lines, in which an irregular spasmodic movement of the blood-corpuscles can be seen. Such a vascularization "should be visible all round the corneal circumference and not in isolated patches, though it need not be present to the same depth in both cornea simultaneously." Here the author is in agreement with Gregory (1943) and Pirie (1943).

* [see also *BMB* 517]

No sign of a deeper corneal vascularization nor any evidence of the consequent development of corneal inflammation or opacities has been encountered. Visual fatigue, but no loss of visual acuity, often accompanies this corneal vascularization. Fissures at the angles of the mouth, a dry scaly skin, a history of dry lips with a tendency to crack and redness of the tip of the tongue, occur in a large proportion of these cases. Riboflavin in adequate dosage is followed by a rapid improvement in the subjective symptoms and a complete cessation of the circulation in the abnormal corneal vessels in 2-3 weeks.

The vascularity of interstitial keratitis is deeper, with larger vessels having the broom-head type of distribution; that following superficial corneal ulceration or inflammation is coarser, localized and easily visible with a binocular loupe.

An abnormal corneal vascularization characteristic of a very mild riboflavin deficiency was found in 7.8% of 422 persons (industrial workers, students, institutional inmates and out-patients). In 13 subjects in which the effect of 10 mg. daily of riboflavin was followed over an adequate period (3-4 weeks) a cessation of the abnormal corneal circulation was observed.

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523

CORNEAL VASCULARISATION IN NUTRITIONAL DEFICIENCY

by T. K. Lyle, T. F. Macrae & P. A. Gardiner, *Lancet*, 1, 393-395, 25/3/44

This paper reports work carried out by three officers of the *Royal Air Force* on the instructions of the Director-General of Medical Services and the Director of Hygiene, Air Ministry. The relationship between corneal vascularization and nutritional status in nearly 4,000 *Royal Air Force* personnel has been studied for over 2 years at 22 localities, 10 in Great Britain, 12 overseas. The overseas stations varied from sub-arctic to tropical desert. At selected stations the effects of supplementary diet were studied.

The nasal, inferior and temporal quadrants of both eyes were examined and four types of vascularity were recorded.* Type A (score 0) a few small vascular twigs only on the limbus; Type B (score 1) increased vascularity of limbus; Type C (score 2) as in Type B but with vascular twigs in clear cornea; Type D (score 3) with vascular loops in a clear cornea.

In Britain, where military rations were considered nutritionally satisfactory, 2,016 subjects were examined throughout the year, the average score was 5.1, and 22% had a score greater than 6. In overseas stations, where the standard of feeding was excellent, the average score was 4.4, with 17% scoring above 6. At a tropical station, where the diet consisted of tinned fruit and vegetables, some poor quality fresh meat, much tinned meat, no fresh fish or eggs and where peanuts and ascorbic acid were issued, the average score was 8.7 with 75% having a score of more than 6.

The effect of various supplements was examined at three stations in Britain, and on two occasions at a sub-arctic station overseas where the findings obtained initially corresponded closely with those in Britain.

- i. Unselected subjects in civilian quarters, and consequently receiving rations similar to those of civilians, were divided into four groups. After 21 days, a significant improvement was detectable in those receiving 4 mg. riboflavin daily, with or without 100 mg. ascorbic acid. Vitamin A, 50,000 international units daily, had no significant effect. This experiment was made early in 1942.
- ii. At a sub-arctic station in the summer of 1942, neither riboflavin 10 mg. daily nor nicotinamide 100 mg. daily produced a significant improvement in the groups taken as a whole, but some subjects with the most definite corneal vascularity did improve, especially on the riboflavin supplements.

* [see *BMB* 517 for a criticism of the notation used.]

- iii. At a station near London in spring 1943, 353 airmen who had been on military rations for some months were divided into three groups: (a) a control group, (b) a second group which received 10 mg. riboflavin daily, (c) a third group which received 3 mg. aneurin, 3 mg. riboflavin, 50 mg. nicotinamide, 10 mg. calcium-pantothenate and 3 mg. pyridoxin. No significant difference was observed in the three groups after 28 days.
- iv. In the summer of 1942, 289 airmen at the sub-arctic station were examined and their diet, which had not been entirely satisfactory, was supplemented with a mixture of highly nutritious foodstuffs which were calculated to add about 4,000 international units vitamin A, 0.5 mg. aneurin, 0.8 mg. riboflavin, 4.5 mg. nicotinamide and 120 mg. ascorbic acid to the daily ration. Re-examination after 5 weeks showed an improvement in the group as a whole, especially in those with initially high degrees of vascularity.
- v. The effect of supplements of liver and kidney to the diet, calculated to about 1.5 mg. riboflavin daily, was followed in 82 airmen for 4 weeks and 50 airmen for 10 weeks in the spring of 1943. No significant improvement was observed.

The authors consider that, although many subjects on excellent dietaries had blood-vessels on the cornea, the average degree of corneal vascularity in a group of subjects is a reliable index of their general state of nutrition. Riboflavin is not the only nutrient concerned in the prevention of corneal vascularization; it appears that other factors present in fruits and vegetables are operative.

524

AMBLYOPIA DUE TO A VITAMIN DEFICIENCY

by P. B. Wilkinson & A. King, *Lancet*, 1, 528-531, 22/4/44

This paper is based on observations made by the authors in Hong-Kong during the latter half of 1940. During this period 15 patients were seen who complained of gradual or sudden onset of dimness of vision. This symptom was associated with soreness of the tongue, giddiness, paræsthesiæ, weakness of the limbs and other manifestations believed to be of nutritional origin. There were no external ocular signs of nutritional deficiency (although it was not possible to make slit-lamp examinations). Temporal pallor of the optic discs was seen in 3 patients, and in a fourth patient who was an undoubted pellagrin there was a left-sided optic atrophy which later became bilateral. In the remaining 11 patients, no abnormality of the optic discs was seen, but in these cases the visual defect had been of shorter duration. In 13 cases the pupillary reactions to light were retarded. In all but 2 cases perimetric examination showed constriction of the visual field. Radiological, neurological and hæmatological findings were not such as to account for the visual defects.

In discussing the ætiology of the condition, the authors draw attention to a deterioration which had taken place in the diet of the social groups from which the patients came. Gradual improvement followed administration of dried yeast in doses of approximately 4 g. 3 times daily. Much more rapid improvement was obtained by nicotinic acid in doses of 100 mg. daily by mouth.

The authors comment that it has for some time been recognized that malnutrition may cause amblyopia, and that their experience in this small series of cases supports this view.

Disease of Teeth and Buccal Cavity

525

MOTTLED ENAMEL, M-HYPOPLASIA AND DENTAL CARIES

by J. D. King, *Dental Record*, 64, 102-110, May 1944

A field investigation was made of the incidence and extent of enamel mottling, M-hypoplasia and dental caries in elementary schoolchildren living in parts of Essex (high fluorine water), Oxfordshire (fairly high fluorine water) and Suffolk

(low fluorine water). The districts were selected in consultation with colleagues (Bowes & Murray, 1935; Lowater & Murray, 1937; Murray & Wilson, 1942; Wilson, 1941) who had already reported various related biochemical, clinical and geological studies in these and other parts of Britain. Many workers in different countries had previously observed that the *general incidence level* of dental caries is usually lower in areas where the population is largely affected by mottling of the enamel, and in such districts the drinking water frequently contains a higher fluorine content than elsewhere. The inference has been that the fluorine intake plays some part in depressing caries susceptibility. It was then reasonable to expect that, using the same diagnostic criteria for mottling, similar findings would be obtained if the *individual teeth* were considered in detail, as distinct from a more general assessment of the state of the mouth as a whole. The apparent absence of any definite relationship between caries and mottling in individual teeth disclosed by the present study was therefore of interest. Further, while the data again showed a definite association between caries susceptibility and certain forms of hypoplasia, the author was unable to trace any association whatever between such enamel defects and presence or absence of mottling. The diagnostic criteria for the three dental conditions considered were as follows:

Enamel Mottling :

(a) For children in the Maldon and Burnham districts of the county of Essex, mottling was classified as :

No mottling (0).

Slight mottling (1): opaque white patches or streaks involving up to one-half of the occlusal or up to one-third of the buccal surface of the teeth.

Medium mottling (2): similar conditions but involving more than one-half of the occlusal or more than one-third of the buccal surface of the teeth.

Severe mottling (3): brown staining of the occlusal or buccal surface of the teeth, with or without pitting.

(b) For children in the Bampton, Hook Norton, Launton and Littlemore districts of the county of Oxfordshire, and Ipswich (Suffolk), enamel mottling was recorded after the methods of Dean (1938) but the degree of mottling was so tabulated as to fall into none, slight, medium and severe grades, in order to conform to tabulation of the data for comparison with extent of caries and hypoplasia.

Dental caries : The method for recording incidence and extent of dental caries was identical with that used by King (1940) the diagnosis being dependent on examination with an illuminated mirror and a probe.

M-hypoplasia : The hypoplasia recorded here excluded the more generally recognized but relatively uncommon form illustrated in most text-books and was confined to the much more prevalent type of defective calcification first described by M. Mellanby (1923, 1927, 1934) and referred to by King (1940) as M-hypoplasia. In estimating the incidence and extent of the latter defect, fully erupted teeth were graded primarily according to the surface roughness of their buccal enamel as tested with a fairly sharp dental probe. As described previously, the grading was then given hypoplasia figures of 0, 1, 2 or 3, the figure 0 indicating "normality" of calcification or no hypoplasia.

Results

i. Essex

Of the 50 children of 12-14 years examined, 46 (92 %) showed some evidence of enamel mottling according to the writer's classification, and this figure would probably have been higher had the diagnostic criteria of Dean (1938) been employed. In this group of subjects, 18 (36 %) were completely free from caries as judged by careful mirror and probe examination. Considering the first permanent molars, and first and second premolars separately and in more detail, the following findings were reported :

First permanent molars : Of the 175 examined, 109 (62 %) were mottled, 55 (31 %) were carious and 84 (46 %) were grade 2-3 (moderately or severely) hypoplastic. As regards the possible association between these three conditions :

of 109 mottled teeth, 26 % were carious ;
of 66 non-mottled teeth, 41 % were carious ;
of 109 mottled teeth 46 % were grade 2-3 hypoplastic ;

of 66 non-mottled teeth, 51 % were grade 2-3 hypoplastic ;
of 84 grade 2-3 hypoplastic teeth, 65 % were carious.
of 91 grade 0-1 hypoplastic teeth, none were carious.

First and second premolars : Of the 361 examined, 264 (73 %) were mottled, 11 (3 %) were carious and 176 (50 %) of 353 teeth * were grade 2-3 hypoplastic. As regards the possible association between these conditions :

of 264 mottled teeth, 2 % were carious ;
of 97 non-mottled teeth, 5 % were carious ;
of 256 mottled teeth, * 46 % were grade 2-3 hypoplastic ;
of 97 non-mottled teeth, 59 % were grade 2-3 hypoplastic ;
of 176 grade 2-3 hypoplastic teeth, 4 % were carious ;
of 177 grade 0-1 hypoplastic teeth, none were carious.

ii. Oxfordshire

Of the 31 children of 12-14 years examined, 30 (97 %) gave evidence of some degree of enamel mottling in one or more teeth per mouth, classified after the method of Dean ; 5 (16 %) were free from dental caries. Individual details were as follows :

First permanent molars : Of the 117 examined, 81 (69 %) were mottled, 65 (56 %) were carious and 79 (68 %) were grade 2-3 hypoplastic. Regarding the possible association between these three conditions :

of 81 mottled teeth, 58 % were carious ;
of 36 non-mottled teeth, 50 % were carious ;
of 81 mottled teeth, 67 % were grade 2-3 hypoplastic ;
of 36 non-mottled teeth, 69 % were grade 2-3 hypoplastic ;
of 79 grade 2-3 hypoplastic teeth, 75 % were carious ;
of 38 grade 0-1 hypoplastic teeth, 16 % were carious.

First and second premolars : Of the 211 examined, 143 (68 %) were mottled, 12 (6 %) were carious and 80 (38 %) were grade 2-3 hypoplastic. As to the association between these conditions :

of 143 mottled teeth, 7 % were carious ;
of 68 non-mottled teeth, 3 % were carious ;
of 143 mottled teeth, 31 % were grade 2-3 hypoplastic ;
of 68 non-mottled teeth, 53 % were grade 2-3 hypoplastic ;
of 80 grade 2-3 hypoplastic teeth, 8 % were carious ;
of 131 grade 0-1 hypoplastic teeth, 5 % were carious.*

iii. Suffolk

From the 200 children of 12-14 years examined, data for the premolar teeth only were recorded and of the 1,409 teeth studied 554 (39 %) were mottled, 190 (13 %) were carious and 593 (42 %) were grade 2-3 hypoplastic. With regard to any association between these conditions :

of 554 mottled teeth, 22 % were carious ;
of 855 non-mottled teeth, 8 % were carious ;
of 554 mottled teeth, 52 % were grade 2-3 hypoplastic ;
of 855 non-mottled teeth, 36 % were grade 2-3 hypoplastic.
of 593 grade 2-3 hypoplastic teeth, 29 % were carious ;
of 816 grade 0-1 hypoplastic teeth, 2 % were carious.

Statistical analysis of the data was then made by the χ^2 † and another test, the results of which can be expressed briefly as follows :

(a) In no instance could any negative or inverse association be found between enamel-mottling and dental caries. Indeed, in the Essex premolar teeth a positive association existed between the two conditions—the more the mottling, the more the caries.

(b) Only in the Oxfordshire premolar teeth was there any negative association between mottling and M-hypoplasia, i.e. the more the mottling the less the hypoplasia.

(c) A positive association was found between M-hypoplasia and caries in all but the Oxfordshire premolar teeth, and in those the caries incidence was too low for any inferences to be drawn with safety.

(d) From (b) and (c) it is apparent that the only instance

* [Of the 361 premolar teeth examined for mottling and caries, 8 were so severely mottled that insufficient enamel was present on the buccal surface to allow hypoplasia grading.]

† [Particulars of this statistical test are to be found in: Fisher, R. A. (1936) *Statistical methods for research workers*, 6th ed. Edinburgh.]

of a negative association between mottling and either of the other two conditions was that between mottling and M-hypoplasia of the Oxfordshire premolar teeth, in which M-hypoplasia and caries were unrelated.

(c) As regards mottling and caries, when analysis was confined to those teeth showing the more severe grades of mottling, there was no significant association between the conditions.

Deciduous dentition

The details relating to the deciduous teeth were not analysed in detail. In Essex, of 50 children under the age of six years, 31 (62 %) showed evidence of enamel mottling in one or more deciduous teeth per mouth, according to the writer's classification. In Oxfordshire, of 39 children between the ages of five and twelve years, 24 (62 %) showed mottling according to Dean's classification. In the latter district, of the 525 deciduous teeth examined 127 (24 %) were affected by some degree of mottling, and of these 62 % were also carious; 141 out of 398 (35 %) non-mottled teeth were carious. A negative association between mottling and caries was again lacking but a positive relationship existed between M-hypoplasia and caries. It was also noted that even in the Essex area, where mottling of the permanent teeth was relatively severe, deciduous mottling was only of minor degree and mainly assumed the form of slight opacity of the tooth cusps, particularly of the posterior teeth.

In a discussion of the findings, it is mentioned that the Essex children's drinking water contained up to 5 parts per million of fluorine: in Oxfordshire there was a varying but generally lesser amount; and in the Suffolk district there was a relatively low fluorine content. Thus, there was confirmation of the results of previous workers as regards a lower general caries incidence level in communities whose drinking water contained comparatively large quantities of fluorine. On the other hand, such findings did not hold good when the caries susceptibility of the individual teeth was considered. The author points out that this apparent anomaly might be related to the fact that there is no evidence that all enamel opacities (other than those due to undermining caries) are always associated with the fluorine intake. Moreover, it is possible that fluorine may exert a protective influence on the teeth not so much by altering the developmental composition and structure of the teeth as by some unknown effect on the saliva or oral micro-flora; if the latter be true then the existence of mottling *per se* might be merely a coincidental reflection of conditions at the time of tooth development. The author concludes: "At the present time it is perhaps safer to limit our speculations to the statement that, with a given fluorine level, the visible demonstration of enamel mottling may depend on the fluorine intake or on other unknown factors on which, in turn, resistance to caries may be dependent or independent."

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526

THE IMPROVED DENTITION OF 5-YEAR-OLD LONDON SCHOOL-CHILDREN: A COMPARISON BETWEEN 1943 AND 1929

by M. Mellanby & H. Coumoulos, *British Medical Journal*, 1, 837-840, 24/6/44

A brief description is first given of the experimental and clinical investigations (Mellanby, 1918, 1923) which led up to the demonstration that susceptibility to dental caries was closely associated with the structure of enamel and dentine and with the calcifying properties of the dietary. This work has been set out in detail in a series of special reports, published by the Medical Research Council (Mellanby, 1929,

1930, 1934, 1936) in which it was shown that vitamin D and other calcifying factors had a protective influence on the teeth. It was therefore advised that, in order to improve the dental health of the population, the dietary of pregnant women, infants and children should be changed to one of higher calcifying quality. It was suggested that this alteration could be best effected by (a) an increased consumption of milk, eggs and other foods comparatively rich in calcifying factors; (b) decreased intake of cereals such as bread, oatmeal and oatmeal preparations; and (c) addition to the diet of cod-liver oil or some other source of vitamins D and A, especially the former. During the last 25 years or so, the British Government has made special efforts to improve the nutrition of expectant and lactating mothers and their offspring and amongst the measures introduced were increased supplies of milk (free or at a much reduced price) and, more recently, of cod-liver oil. Such improvements were, in fact, precisely those which Mellanby's investigations had indicated would have a beneficial influence on dental health, and therein lay the reason for the present study. Already, in 1929, a dental examination had been made of 1,300 London children in which the incidence of caries and hypoplasia was recorded (Board of Education, 1931) and in 1943 it became possible to study these conditions in a group of London children of comparable age and living in the same districts; on both occasions the same examination criteria were adopted. The following results show that changes in both surface structure of the teeth and caries incidence have occurred between 1929 and 1943—the structure of the teeth has become better and the amount of caries has been reduced.

Table I summarizes the findings as regards dental structure. The term M-hypoplasia refers to roughness of the buccal

TABLE I—INCIDENCE OF M-HYPOPLASIA IN DECIDUOUS TEETH

	Total children	Percentages showing:			
		none	little	some	much
1943	1,571	1.2	18.1	47.4	33.3
1929	1,139	0	7.8	33.6	58.5

enamel compared with the enamel texture of puppies fed on diets relatively rich in vitamin D and containing the necessary calcium and phosphorus, such hypoplastic defects having been found to be closely related to caries susceptibility (Mellanby, 1918, 1923, 1929, 1930, 1934, 1936; Board of Education, 1931; King, 1940). It can be seen that, while few children even now have a full complement of perfectly calcified teeth, there has been a considerable change for the better during the past fourteen years. In Table II the findings are given when the schools are divided according to their

TABLE II—INCIDENCE OF M-HYPOPLASIA IN DECIDUOUS TEETH AT THE DIFFERENT SOCIAL LEVELS

Social grading of school	Total children	Percentages showing:			
		none	little	some	much
Highest grade (B +)					
1943 ...	190	0.5	25.8	49.0	24.7
1929 ...	133	0	12.8	30.9	56.4
2nd grade (B)					
1943 ...	582	1.0	14.8	50.2	34.0
1929 ...	423	0	9.9	36.4	53.7
3rd grade (B -)					
1943 ...	556	1.8	18.0	45.1	35.1
1929 ...	190	0	4.7	30.0	65.3
4th grade (C)					
1943 ...	243	0.8	20.2	44.9	34.2
1929 ...	393	0	5.4	33.3	61.3

estimated social status. There are no great differences in these groups in 1943, although the tendency is for the highest grade schools (B +) to have teeth of rather better structure than the schools in the other three grades. In 1929 there was a suggestion that the quality of structure was worse in the lower-grade schools.

in Table III the incidence of dental caries in the two investigations is set out, the examination criteria being as far

TABLE III—INCIDENCE OF DENTAL CARIES IN DECIDUOUS TEETH

	Total children	Percentages showing :			
		no caries	little caries	some caries	much * caries
1943	1,604	22.4	25.9	22.4	29.3
1929	1,293	4.7	11.7	20.8	62.8

* Only 6 % of the children in this category in 1943 would correspond with the C6 group (very bad caries), compared with 54 % in 1929.

as possible identical. It is clear that a considerable improvement in dental health has occurred since 1929. Actually the improvement is even greater than might appear at first sight, as in 1943 only about 6 % of those in the "much caries" group could be classed in the "very bad caries" group (differentiated in 1929) compared with 54 % in the earlier study, which included a number of edentulous children. Separation of the children according to social level (Table IV) indicates that in 1943 there was distinctly less caries in the B + schools than

TABLE IV—INCIDENCE OF DENTAL CARIES IN DECIDUOUS TEETH AT THE DIFFERENT SOCIAL LEVELS

Social grading of school	Total children	Percentages showing :			
		No caries	Little caries	Some caries	Much caries
Highest grade (B +)					
1943	193	29.5	28.5	21.2	20.7
1929	147	6.1	17.7	15.6	60.6
2nd grade (B)					
1943	596	20.8	27.7	22.0	29.5
1929	480	6.5	11.3	22.6	59.6
3rd grade (B -)					
1943	569	22.9	23.6	21.1	32.5
1929	210	3.8	10.5	22.9	62.8
4th grade (C)					
1943	246	19.5	25.2	27.2	28.1
1929	456	2.8	10.5	19.5	67.1

in the other three grades. In 1929 there was a slight tendency for caries to increase from the better to the poorer schools. In addition to the main survey, a subsidiary group of 266 children, not comparable with those in any of the 1929 schools, was examined in 1943; the findings were in general similar to those in the main 1943 investigation.

Other results, not considered in so much detail, concern *arrested caries* and *association of M-hypoplasia and caries*. It was found that, in at least some teeth, 28 % of the 1943 subjects showed evidence of arrest of the carious process. An indication was also obtained that some post-eruptive influence (direct or indirect) appeared to have qualified to some extent the previous close association between the surface structure of the teeth and their susceptibility to decay.

In a discussion of the results the authors summarize their findings as follows:

"The data obtained in this survey show clearly that there has been a distinct improvement since 1929 in the dental condition of 5-year-old children attending London County Council elementary schools. The quality of the teeth is now better; in 1943, 19 % of the children had teeth of good structure, compared with 8 % in 1929, while the percentages with very defectively formed teeth (i.e., teeth with 'much' M-hypoplasia) were 33 and 58 respectively. The reduction in the incidence of dental decay is even more striking: in 1943, 22 % of the children were 'caries-free,' compared with 5 % in 1929, while only 29 % had 'much' caries in 1943 as compared with 63 % in 1929. When the schools were grouped according to social status there was little difference in dental condition as regards both structure and caries between the various grades, though the teeth tended to be rather better in the highest-grade schools in 1943 and in the two highest grade schools in 1929."

They go on to point out that, as the teeth of the 1943 5-year-old children were in the main formed in the immediate

pre-war years and the first year of the war, the cause of the improvement in these particular children must be sought among factors operative at and since that time, and contrasted with the conditions in the years 1922-29, when the teeth of the children examined in the previous survey were developing. The possibility that the changed dietary, including increased intake of vitamin D and calcium, the provision of cheap milk and cod-liver oil to infants and young children, together with the addition of vitamins A and D to the margarine and of calcium carbonate to the bread, has played a significant part in decreasing caries-susceptibility is also discussed. In this respect the improved dental structure would seem to afford some evidence, but the authors are inclined to believe that some other unknown factors have also been at work. Among the latter they mention the possibility that changes in the carbohydrate intake or a greater use of the tooth-brush may be here involved but rightly point out that "the basis of these suggested factors [i.e. carbohydrate intake and tooth-brushing] is too insecure at the present time to allow their effects to be assessed adequately." In conclusion, the authors state that "It is possible that the elimination of dental caries may not be attainable until its immediate cause is known, but even without this knowledge it is probable that a continuation and extension of the present nutritional policy and its more whole-hearted adoption by the public would bring about further improvement in the architecture of the teeth and in their subsequent resistance to decay."

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527

FLUOROSIS AND DENTAL CARIES ON TYNESIDE

by R. Weaver, *British Dental Journal*, 76, 29-40, 21/1/44

The teeth of 500 children aged five years and 500 children aged twelve years were examined in each of two towns in North-East England. Special attention was paid to the incidence and extent of dental caries and enamel mottling. Two methods were used for recording caries: (i) a modified form of that employed by M. Mellanby (1934), which allowed the comparison of groups of subjects by means of "average caries figures"; and (ii) another adapted from American workers in which the conditions found were expressed as the average number of teeth per child which were decayed, missing or filled ("average DMF"). For mottling, the criteria were as follows: (a) no mottling; (b) questionable mottling, paper-white patches on the enamel of only one tooth; (c) very slight mottling, similar patches involving less than 25 % of the surface of two or more teeth; (d) slight mottling, similar conditions involving 25-50 % of the enamel surface of two or more teeth. The more severe forms of mottling, including pitting, brown staining and change in tooth contours, were not found.

The *state of nutrition* of the children was also roughly assessed according to the four nutritional categories suggested some years ago by the Board of Education, viz.: A, excellent; B, normal; C, slightly sub-normal; and D, bad. Finally, the water supplies for the two towns were analysed with particular reference to their fluorine content, and an account was given of the economic, sociological, geographical and other conditions obtaining in North and South Shields.

Results: The towns from which the examination subjects were selected were only about 500 yards apart, being separated by the River Tyne, but a considerable difference was found in the caries susceptibility. The only other difference which the author could determine was in the fluorine content of the water supplies of the communities north and south of the river. In North Shields, the drinking water contained less than 0.25 parts per million of fluorine; in South Shields the water contained approximately 1.4 parts per million of

fluorine. The detailed results may be briefly summarized as follows:

i. Extent of caries in deciduous teeth of 5-year-old children.

	North Shields	South Shields
Number of teeth considered ...	3,279	1,951
Average caries figure ...	16.0	9.5
Average DMF ...	6.6	3.9

ii. Extent of caries in permanent teeth of 12-year-old children.

	North Shields	South Shields
Number of teeth considered ...	2,133	1,195
Average caries figure ...	10.0	5.1
Average DMF ...	4.3	2.4

The incidence of dental caries in the permanent teeth in South Shields was only 56 % of that in North Shields.

iii. No case of definite mottling of the deciduous teeth was seen in any of the 1,000 children examined.

iv. No relationship could be found between dental caries and mottling, as shown for the permanent teeth of 500 children:

	Number of children	Number caries-free	Average caries figure	Average DMF
Mottling absent ...	366	104	5.0	2.3
„ questionable ...	28	3	6.1	2.7
„ very slight ...	88	18	5.5	2.6
„ slight ...	18	4	5.3	2.3

The author then discusses his findings with reference to those of previous workers and, though he appears to believe that the higher fluorine concentration in South Shields was related to the lower caries susceptibility, he makes no suggestion as to how the increased resistance of the teeth is brought about.

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528

FLUORINE AND DENTAL CARIES: FURTHER INVESTIGATIONS ON TYNESIDE AND IN SUNDERLAND

by R. Weaver, *British Dental Journal*, 77, 185-193, 6/10/44

In a previous paper (Weaver, 1944) the author reported the low incidence of dental caries in children of South Shields as compared with the incidence in the neighbouring town of North Shields. The drinking water in South Shields had a higher fluorine content. Examination of available statistics showed no evidence of superior general health of the South Shields population. A further survey of the dental condition of children of 14 years and over showed smaller differences in the incidence of caries in areas having a water supply of differing fluorine content. The incidence of untreated caries in mothers from North Shields and South Shields did not differ appreciably.

The author concludes that fluorine (if this is indeed the caries-inhibiting factor) postpones, but does not prevent, dental caries. He argues from data presented in the paper that the caries-inhibiting factor exerts its influence on the teeth during the pre-eruptive period. If this is true, the rational basis for the topical application of fluorine solutions to the teeth in caries prophylaxis would seem to be doubtful.

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¹ Weaver, R. (1944) *Brit. dent. J.* 76, 29

¹ [see *BMB* 527]

529

BLEEDING GUMS AND GINGIVITIS IN NAVAL RATINGS

by A. C. Macdonald, *Lancet*, 2, 697-699, 4/12/43

In this paper are reported the results of a survey of the incidence of bleeding gums and gingivitis in otherwise physically fit naval personnel on active service in three small sea-going ships and a depot ship. The men of the largest of the three sea-going craft were observed over a period of 14 months, the other three groups on only one occasion. All the subjects were on a full service diet and had a considerably better fruit

and vegetable content of the diet than the members of the armed forces or civilians resident in England. Whilst at their bases abroad daily issues of fruit juices were made, and in the two smaller ships the men were encouraged to take multivitamin tablets [composition not stated]. In all, 614 men were examined, of whom 6.5 % were edentulous, 21.8 % showed a mild gingivitis and 6.7 % a severe gingivitis. The incidence of gingivitis was higher in the sea-going ships and in the over-30-years age-group. In the group of 156 men kept under observation for 14 months, 17 men reported their condition spontaneously; of these 11 had gingivitis, 4 were cases of acute ulcerative Vincent's infection of the gums and 2 had both symptom-complexes; all of these last 6 cases had a history of sore and bleeding gums. Examination of the whole ship's company disclosed 24 more cases of gingivitis, of whom 6 were undergoing treatment for syphilis with intravenous organic arsenicals.

Treatment consisted in removal of the tartar by scaling. Intravenous arsenicals gave a good response in 8 days in acute ulcerative gingivitis or in those cases with faucial infection. The chronic cases responded most readily to 10 % chromic acid followed in one minute with hydrogen peroxide (10 vol.) applied on cotton-wool pledgets. A normal mucoperiosteal junction was obtained in from 5-7 days in mild cases, and 7-12 days in the severe forms.

During a two months' observation a 22 % recurrence was observed.

530

GINGIVAL DISEASE IN GIBRALTAR EVACUEE CHILDREN

by J. D. King, A. B. Francklyn & I. Allen, *Lancet*, 1, 495-498, 15/4/44

In the autumn of 1941 a high incidence of fairly severe gingivitis was found by Francklyn (1941, 1942) in a group of 946 children evacuated to London from Gibraltar. As a result of this finding, Dr. King undertook, at the request of the Ministry of Health, a more critical investigation in a smaller group of 135 Gibraltar children of 10-14 years. Of these, 40 % were affected by lesions simulating the earlier phases of ulcerative gingivo-stomatitis (Vincent's disease) as compared with 1-2 % of 403 English children. The fact that the lesions were prevalent in groups of Gibraltarians living in widely separated parts of London, between whom there was little or no contact, precluded an infective basis for the disease. Moreover, although these children attended London elementary schools and mixed with the English pupils, the latter were singularly free from the ulcerative disease. General mouth hygiene, occlusion of the teeth, incidence and extent of caries, and tartar deposition did not differ significantly from such conditions in more than 2,500 English children examined by King at various times during the past six years. No obvious evidences of deficiency of vitamins A, C or riboflavin could be found. Since, therefore, the resemblance to Vincent's disease seemed to be the most likely clue to the nature of the disorder, it was decided to carry out a therapeutic trial of the effects of nicotinic acid administration, previously found to be of value in the treatment of gingival ulceration in adults (King, 1940a, 1943). Lack of co-operation on the part of both parents and children led to restriction of the number of subjects for the test. Eventually, 36 boys receiving the same basal dietary were divided into four groups as follows:

Group A. Each of 10 affected children was given 50 mg. of nicotinic acid daily for the five school days of two successive weeks: the vitamin was swallowed in tablet form at approximately the same time each day during the school morning session.

Group B. Each of 11 affected subjects received local hygienic treatment for five consecutive days of one week, as follows:

1st day: Application of chromic acid (10 %) to all gingival tissues, healthy as well as diseased, followed immediately by vigorous rinsing of the mouth with 10-vol. H_2O_2 (1:4 dilution).

2nd day: Removal of tartar by scaling, followed by further application of chromic acid and rinsing with H_2O_2 .

3rd day: Removal of any remaining tartar and vigorous syringing with H₂O₂.
 4th & 5th days: Syringing with H₂O₂.

Group C. Each of 10 affected boys was given 50 mg. of nicotinic acid daily for the five school days of two successive weeks plus the local hygienic treatment (as for group B) for the five school days of the first week.

Group D. A further 5 boys affected by the disease formed an untreated control group. Precautions were taken to prevent their receiving any medical or dental treatment elsewhere.

The children were carefully examined and detailed records were made of their mouth condition (a) before the test period, (b) two weeks after the test began, and (c) four weeks after completion of treatment. As the investigation was on a relatively small scale, the results were expressed in terms of the individual gum regions rather than of the mouth as a whole. The method of classifying the lesions was developed from that used by King (1940b). The findings are briefly summarized in Table I, where gingival disease is shown as M + (slight marginal), M + + (more marked marginal), P + (slight blunting) and P + + (more marked papillary disease involving slight ulceration).

TABLE I—RESULTS EXPRESSED IN TERMS OF COMPLETE RECOVERY OF GUM REGIONS ORIGINALLY AFFECTED BY THE FOUR GRADES OF DISEASE
 A = Nicotinic acid ; B = Local hygienic ; C = Combined treatment ; D = Untreated controls

Groups	No. of regions originally affected	Regions showing complete recovery			
		After 2 weeks ¹		After 6 weeks ²	
		Number	%	Number	%
M+ Lesions					
A	15	10	66.7±12.17	15	100.0
B	35	31	88.6± 5.37	32	91.4±4.74
C	21	19	90.5± 6.40	21	100.0
D	6	0	...	0	...
M++ Lesions					
A	52	30	57.7± 6.85	36	69.2± 6.40
B	49	22	44.9± 7.11	33	67.3± 6.70
C	69	57	82.6± 4.56	64	92.8± 3.11
D	31	0	...	3	9.7± 5.32
P+ Lesions					
A	23	12	52.2±10.42	14	60.9±10.02
B	41	9	22.0± 6.47	10	24.4± 6.71
C	22	4	18.2± 8.23	12	54.5±10.62
D	14	0	...	0	...
P++ Lesions					
A	28	6	21.4± 7.75	11	39.3± 9.23
B	13	0	...	0	...
C	19	6	31.6±10.67	6	31.6±10.67
D	10	0	...	0	...

¹ [At completion of treatment ; untreated controls re-examined on same date.]
² [At follow-up examination (no further treatment).]

This table shows the percentages of gum regions originally affected which completely recovered after 2 and 6 weeks respectively ; the figures are tabulated to indicate the relative effects of the three treatments compared with the controls for each type of lesion. Local hygienic measures produced good results in the slight (M +) lesions but were less effective as the severity of the disease increased. In the most severe (P + +) lesions, local treatment produced no complete recovery, whereas the nicotinic acid alone and the combined treatments showed a significant 21 % complete recovery. It was, however, necessary to obtain some finer assessment of improvement or otherwise than that indicated by complete recovery. It was observed that in untreated cases progression from M + to P + + disease often occurred, so that by marking "normality" as 0, M + as 1, M + + as 2, P + as 3, and P + + as 4, a total disease figure per mouth could be calculated ; from this an average disease figure was

obtained by dividing the total disease figure by the number of regions which were or could be affected. Table II gives the average disease figures obtained by this method for

TABLE II—COMPARISON OF AVERAGE DISEASE FIGURES
 (M+ = 1, M + + = 2, P + = 3, and P + + = 4)
 A = Nicotinic acid ; B = Local hygienic ; C = Combined treatment ; D = Controls

Group	At 1st exam. (a)	After 2 weeks (b)	After 6 weeks (c)	Difference between (a) and (b)	Difference between (a) and (c)
A	1.21	0.40	0.41	-0.81±0.10	-0.80±0.11
B	1.20	0.47	0.44	-0.73±0.10	-0.76±0.10
C	1.19	0.26	0.22	-0.93±0.09	-0.97±0.09
D	1.15	1.45	1.33	+0.30±0.17	+0.18±0.17
Comparing A and D ...				1.11±0.19	0.98±0.20
Comparing B and D ...				1.03±0.19	0.94±0.19
Comparing C and D ...				1.23±0.19	1.15±0.19
Comparing A and B ...				0.08±0.14	0.04±0.15
Comparing A and C ...				0.12±0.14	0.17±0.14
Comparing B and C ...				0.20±0.14	0.21±0.14

(a) initial examination, (b) after two weeks, and (c) after six weeks ; and the differences between (a) and (b) and between (a) and (c). The controls, so far from showing improvement, deteriorated and, comparing them with each of the types of treatment, the differences are all statistically significant. For early lesions, local measures were effective but were progressively less satisfactory as the lesions became more severe. Treatment with nicotinic acid alone or combined with local hygienic methods gave better results than the local treatment alone, particularly for the more severe lesions ; the results with nicotinic acid were, however, probably relatively delayed. The vitamin combined with local measures appeared to be more effective than nicotinic acid alone.

Finally a two-months trial of the effects of treating the lesions by administration of food-yeast (*Torula utilis*) was conducted in a further group of 41 affected Gibraltar children living in hostels on the same basal dietary. The test involved the daily addition to the diet of 3.5 g. of food yeast for 24 children ; the remaining 17 controls received no treatment or supplement. The results (Table III), expressed more simply than for the main investigation, show that the yeast

TABLE III—EFFECT OF YEAST SUPPLEMENTS ON THE GUM LESIONS

Group	No. of children with different grades of gingivitis	
	before test	after test
E. Yeast supplement, 3.5 g. daily (24 children) ¹	P ... 13	P ... 2 M+ ... 3 Nil ... 8
	M++ ... 5	M+ ... 1 Nil ... 4
	M+ ... 6	M+ ... 1 Nil ... 5
F. Untreated controls (17 children) ¹	P ... 11	P ... 6 M++ ... 4 M+ ... 1
	M++ ... 1	M++ ... 1
	M+ ... 5	M++ ... 3 M+ ... 1 Nil ... 1

¹ [In these children the P + and P + + lesions were not separated. The condition here recorded for each child refers to the most severe gum disease present in one or more of the regions examined.]

supplements considerably improved gingival health, but it was impossible to determine whether the beneficial effects were due to the small nicotinic acid content (1.4 mg. daily) or to some other component.

The authors conclude that the findings of the investigation as a whole indicated that deficiency of the nicotinic acid component of the vitamin B₂ complex played some part in the aetiology of the ulcerative lesions in the Gibraltar children studied, but that other undetermined factors existed, more particularly in the milder M-type disease. In support of the latter belief, the main results of an unpublished investigation (by J. D. King) of non-ulcerative gingivitis amongst young factory workers are cited. In an untreated control group, 50 % of 32 M + and 3 % of 32 M + + lesions recovered during an observation period of four weeks. The respective recovery figures in two other groups receiving nicotinamide (200 mg. daily) and ascorbic acid (200 mg. daily) for two weeks were 91 % of 54 and 63 % of 55 for the M + lesions, and 67 % of 41 and 17 % of 24 for the M + + lesions.

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¹ [see *BMB* 104]

531

INCIDENCE OF GINGIVITIS IN THE ROYAL AIR FORCE

by G. A. Smart, *British Medical Journal*, 2, 242-244, 19/8/44

The author carried out a survey of the gums of random samples of airmen and airwomen from each of four Royal Air Force stations. The incidence of "gingivitis" was approximately 40 % of the 1,204 subjects examined, according to the criteria adopted. Of the affected personnel, 75.4 % were said to have non-ulcerative gingivitis, 8.9 % healed gingivitis, 15.0 % chronic ulcerative gingivitis, and 3.0 % acute ulcerative lesions superimposed on pre-existing inflammation. Unfortunately, while a detailed description is given of the meanings of these disease terms, the standard used for "normality" is less clearly indicated. Moreover, the author considers that one of the characteristics of healed gum lesions is absence of the interdental papillae. This would imply that the disease has to progress to atrophy of these structures before signs of healing become evident, which is clearly not true in many cases. Apart from one bomber station where the women's gums were worse than the men's, no significant sex differences were found. As would be expected, the incidence of gingival disease became higher as age increased. An indication was also found that the pre-Service social status of the personnel had some influence on susceptibility to gum disease, the condition being less prevalent in the higher-income groups, and the author suggests that both dietetic factors and differences in personal hygiene may be concerned here. Finally, with regard to differences in gingivitis incidence among different categories of personnel, gum disease in the air-crews was significantly less than in the other groups. On the other hand, the incidence among those engaged in the preparation of food and associated duties was found to be significantly higher than among the remainder, excluding air-crews. He then remarks: "If the condition is infectious this finding is obviously important," but up to the present time, at least, there is no reliable evidence that most gingival lesions are infective and indeed there is much evidence to the contrary, so that this finding would scarcely seem relevant. There seemed to be no relation between the incidence of gingivitis and length of military service, but significant differences were found among the various trade groups, the incidence being lower among those who were more highly paid. No comments are made concerning the possibility that the relative amount of dental treatment received by the examinees might have had some influence on the gingival condition in the various groups. Some comparisons are made between the general findings and the investigations of gingival disease made by Semple, Price-Jones & Digby (1919), Whittingham (1932), Roff & Glazebrook (1940) and Macdonald (1943) among different Service units, in which the incidence figures ranged from 17.6 % to 28.6 % (uncorrected for age variations) according to the varying examination methods employed. In the author's results a method of age-correction was used.

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¹ [see *BMB* 529]

532

INCIDENCE OF BLEEDING GUMS AMONG R.A.F. PERSONNEL AND THE VALUE OF ASCORBIC ACID IN TREATMENT

by W. P. Stamm, T. F. Macrae & S. Yudkin, *British Medical Journal*, 2, 239-241, 19/8/44

An investigation was made between October 1941 and May 1942 for the purpose of ascertaining the incidence of bleeding gums in the Royal Air Force and of assessing the value of ascorbic acid in the treatment of this condition. In addition, the ascorbic acid content of the food as served to the airmen in the messes was determined by the dichlorophenolindophenol method of Harris & Olliver (1942) during one week of the experimental period at each of the three stations considered.

Experiment i: The total number of personnel examined at the three stations was 1,791, and of these 344 (19.2 %) had some degree of bleeding of the gums. The incidence varied between the stations and between different classes at the same station, but not to any significant extent. Of those with bleeding gums, 119 were given 200 mg. ascorbic acid daily for 7 days followed by 100 mg. daily for 14 days; and 131 received dummy tablets flavoured with tartaric acid, forming the control group. Precautions were taken to ensure that no other form of treatment was given to these men during the experimental period.

No significant difference could be found between the two groups; ascorbic acid did not have a more beneficial effect than the dummy tablets, and indeed the latter had a slightly better effect. It was also of interest that in 5 of the 119 subjects having ascorbic acid, and in 9 of the 131 controls, ulcerative gingivitis developed during the experimental period. The average daily intake of the airmen at this time (Oct.-Nov. 1941) was 26 mg. ascorbic acid; later, in the Spring of 1942, the intake was 17 mg.

Experiment ii: At another Royal Air Force station, in April 1942, 122 out of 571 airmen (21.3 %) had bleeding gums. Of the affected number, 68 were given 150 mg. ascorbic acid for 20 days, and 48 who received the dummy tablets served as controls. Again, the dummy tablets were rather more effective than the vitamin supplements.

Experiment iii: At the same station as in experiment ii, 600 other airmen were examined for bleeding gums three times at intervals of three weeks during April and May 1942. Almost exactly the same percentage showed bleeding at each examination (about 20 %), but only 57 of the 122 with hæmorrhages at the initial inspection had bleeding at the final one. At the second examination the gums of 48 subjects (39 %) had stopped bleeding entirely—about the same number as showed improvement in experiments i and ii—but at the same time 37 of the remainder had started to bleed. Similarly, at the third examination 34 had stopped bleeding while 41 had started. The authors felt justified in concluding that in Royal Air Force personnel in this country ascorbic acid is valueless in the treatment of bleeding gums, and that the incidence of such lesions is not related to the ascorbic acid intake.

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533

STOMATITIS DUE TO RIBOFLAVIN DEFICIENCY

by H. E. Jones, T. G. Armstrong, H. F. Green & V. Chadwick, *Lancet*, 1944, 1, 720-723, 3/6/44

In a North African camp containing 10,313 men of various races (Arabs, Berbers, Negroes, Ethiopians, Turks and

Europeans), 1,746 (16.93 %) were found to be affected by a form of stomatitis. The signs and symptoms included sore tongue, sore lips, some degree of trismus from the cheilosis, and excessive salivation; except for their mouths, the patients felt in excellent health. The conditions cleared rapidly on addition of milk, meat and eggs to the diet, or on administration of riboflavin or yeast.

Clinical findings: Lesions of the tongue began with sore, reddened areas at the tip and/or edges of the organ, where the papillae were less conspicuous than usual. This process then spread backwards in a triangular pattern with the base of the triangle at the tip and the advancing apex central and pointing towards the root of the tongue; small areas of atrophy were often present in the unaffected areas. As atrophy advanced, the redness diminished, and during this intermediate stage alterations of the papillae were in general of two types: (a) enlarged, pale, flat-topped filiform papillae ("white mushrooms"); and (b) enlarged, less flattened fungiform papillae with red centres ("red mushrooms"). In more advanced cases the tongue became increasingly smooth and shiny and fissures began to develop, radiating outwards from the median raphe. Sometimes, however, fissures were seen at much earlier stages or small, shallow, painful ulcers occurred. In the final stage the anterior part of the tongue was completely smooth and atrophic, with loss of papillae, wasting, sharpened edges and tooth indentations. Occasionally a few petechial haemorrhages were observed on the under surface of the organ, but the magenta colour of the tongue described by others as characteristic of riboflavin deficiency was not seen. In their later phases the tongues did not apparently differ from those of pellagrins.

In addition to the usual clinical examination, the slit-lamp microscope was employed for studying the above changes in the tongue papillae as compared with "normal controls." With the aid of this instrument the authors found that in the affected subjects the characteristic condition was denudation of the filiform papillae of their filamentous processes and subsequent atrophy of the papillae themselves. The slit-lamp microscope showed the earliest alteration (loss of the filiform processes) in tongues which might appear macroscopically normal and might indeed have unusually prominent papillae, giving a false impression. The tongues were divisible into two groups, atrophic and hypertrophic, of which the atrophic were much more common. The tip of the tongue showed the same changes in both groups, but there were differences in the central area of the organ. At the tip, both sets of papillae were somewhat swollen and their margins came together, forming a more or less smooth pavement without denudation. The fungiform papillae sometimes became opaque, with their contained capillaries hardly visible through the thinned and opaque epithelium covering them. The filiform papillae lost their hairs and were seen as naked structures with opaque, pearly-white epithelium obscuring the blood-vessels; they began to resemble the fungiform papillae in shape, making it difficult to differentiate between the two. In the central area the atrophic type showed three stages: (i) denudation of hairs; (ii) atrophy of the papillae themselves; and (iii) complete disappearance of the papillae, leaving an entirely smooth surface through which the linear streaks of the underlying vessels were indistinctly seen. For the hypertrophic variety of lesion the same changes occurred except that during stage (i) the filiform papillae, besides losing their hairs, actually grew larger; they came to resemble the fungiform papillae closely, but were distinguishable by their pearly-white opacity and the invisibility of their blood-vessels. Finally, sections from two affected tongues were compared with histological preparations from a normal one. The changes observed included flattening of surface papillae, loss of ramification of down-growing epithelial processes, and complete cessation of epithelial growth.

As regards the lips and cheeks, the second important change in the syndrome described was an angular stomatitis which was not infrequently unilateral in distribution. This started as a tiny, painful, raw, red area at the commissure of the lips where the mucous membrane joins the skin. The red area spread along the mucosa of the cheek and lower lip but tended to be confined to a size of less than 1 cm.². Quite early this became covered with white epithelium (like blotting-paper), which could not be scraped off easily, and the latter sometimes extended to form large sheets, criss-crossed by cracks and resembling dried mud which had flaked. Concurrently, small painful fissures often developed in the skin

at the corners of the mouth. The changes tended to spread to the mucosa of the lower lip, and in several cases fairly large, painful, oval ulcers developed. A less common finding on the lower lip comprised a group of small papular swellings, each of pin-head size and slightly paler than the surrounding reddened mucosa. These lip changes nearly always appeared near the skin margin, the gingival parts being spared. In only 20 of the 1,746 cases affected were lesions seen on the mucous membrane of the upper lip, and in all but one of these exceptions they were small. Some of the subjects with lips involved could be detected, before the mouths were opened, by virtue of a fine white line, due to epithelial alterations, visible from the angles of the mouth along the labial margins.

The incidence of lesions of the palate was about 5 %, a common site being well back on the hard palate, but occasionally there was a large area of redness near the alveolar margin. Their form was similar to those on the lips but their outline was always serpiginous and plaques were never seen; the edges were overhung by a rim of sodden, white epithelium.

Hospital investigation: A group of cases was then admitted to a British general hospital for more detailed study; their ages varied from 21 to 48 years. Routine and special examinations revealed the following findings:

None showed wasting, their skin was glossy and healthy and no pellagrous changes were seen; four had slight seborrhœic overgrowth in the nasolabial folds, but this sulphur-granule appearance also occurred in mild degree in 20 % of 300 controls; nails were well formed and strong, without koilonychia or fissuring; erythrocyte and leucocyte counts (20 cases) gave no data of significance; stools contained no excess of fatty acids or undigested food; sigmoidoscopy (10 cases) showed no abnormalities in bowel mucosa, and anal canals and perianal regions were normal; fractional test-meals (21 cases) indicated that free HCl was normal in 12 and high in 6, while 3 had achlorhydria; blood-urea (10 cases) varied from 18–42 mg. per 100 cm.³; ten men, chosen at random, gave negative Kahn tests; eighteen out of 20 men had healthy gums; there was some sponginess in 2 and dental caries in only 1; seventy-five cases were examined for vascularising keratitis and all showed increased vascularity in mild degree, but all were suffering from trachoma (common in N. Africa); swabs from mouths of 30 cases showed moderate numbers of Vincent's organisms in 8 and monilia in 1; there was nothing to suggest that infection was a cause of the condition and local treatment with copper sulphate (5 %) "protargol" (5 %), and flavine (2 %) produced no improvement.

Relation to diet: Attention was then directed to the diet of the affected subjects, and it was noticed that the lesions began to appear about two months after dietary alterations had reduced the intake of certain food essentials; a table is given showing the approximate daily intake of constituents before and after the changes. It was found that the condition responded rapidly on adding milk, meat or eggs to the diet. Other remedies tried were:

Calcium lactate, given in 30-grain [about 1.8 g.] doses daily to 10 men for 10 days—no improvement;

Red palm oil, containing 3,800 international units vitamin A per ounce [about 28 g.], given in 1/10 ounce doses daily to 200 men for ten days—no improvement;

Oleum vitamini (B.P.), a dose containing 2,250 international units vitamin A and 250 international units vitamin D daily for ten days—no improvement;

Yeast, fresh or dried, given in doses of ½ ounce daily—rapid cure, causing the soreness to diminish or vanish within 4 days and most of the mouth changes to disappear in 7–10 days.

Thus the aetiological factor of the stomatitis was evidently related to deficiency of some constituent of milk, meat, eggs and yeast. Further trials showed that, while nicotinic acid was of no benefit in daily doses of 600 mg. for five days (5 cases treated), administration of riboflavin (10 mg. twice daily) effected striking improvement in 6 patients compared with 14 untreated controls. Finally, when the camp population was given a diet calculated to increase the riboflavin content to about 1.73 mg. riboflavin daily, the stomatitis ceased. [N.B. As the work was done in a desert hospital, no works of reference were available and the authors were unable to discuss their findings in relation to those of previous investigators in this field.]

Nutrition and Physical Fitness

534

VITAMINS AND PHYSIOLOGICAL FUNCTION

by G. N. Jenkins & J. Yudkin, *British Medical Journal*, 2, 265-266, 28/8/43

Harper, Mackay, Raper & Camm (1943) at Manchester demonstrated improvement in certain physiological functions in cadets who had been given a short period of supplementary feeding with vitamins. The present authors, of *St. Bartholomew's Hospital Medical College* and the *Dunn Nutritional Laboratory*, Cambridge, repeated these experiments on a group of Cambridge elementary-school children who had been receiving vitamin pellets for a year. Altogether 178 children were examined, comprising 80 12-year-old girls, 76 12-year-old boys and 22 11-year-old boys. About half in each group—alternate children from the school register—had received vitamin pellets daily at school, and the remainder received control pellets. The vitamin pellets contained 5,000 international units vitamin A, 1 mg. vitamin B₁, 25 mg. vitamin C and 500 international units vitamin D. The children were living and eating in their own homes except for some who had dinner at school. Allowing for week-ends and holidays, the average supplement over the year was roughly half the reputed daily requirements of these nutrients; apart from the vitamin B₁, which Harper *et al.* did not administer, the children were obtaining less of the supplemented vitamins than the subjects at Manchester. The functions tested were the same as those used by the Manchester workers, namely, average resting pulse-rate, average vital capacity, average vital capacity compared with body surface, average breath-holding time and average endurance test (the latter being represented by the time in seconds during which the subject could maintain, after full inspiration, a column of Hg at a level of 40 mm.). The children had also been measured for gain in height and weight, strength of grip, haemoglobin, intelligence, educational attainment and dark-adaptation (Yudkin, 1943). There had been no improvement in these tests of the supplemented group over the control group.

The application to these children of the tests used by Harper *et al.* showed that there was no significant difference between the two groups. Half of the 12-year-old boys were also examined by the same tests three days after the completion of a vitamin-C saturation test, during which they received an average of 350 mg. daily of vitamin C. No difference could be detected between the saturated and the non-saturated group.

The authors emphasize that the absence of effect of the supplements in their subjects need not be interpreted as contrary to the findings of Harper *et al.*, but they indicate that the improvement of physical efficiency by vitamin supplements cannot be regarded as being generally applicable to all groups.

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² [see *BMB* 101]

535

LEVELS OF VITAMIN A AND C NUTRITION IN GLOSSOP SCHOOL-CHILDREN AND EFFECT OF DEFICIENCIES ON THEIR PHYSICAL CONDITION

by G. Kohn, E. H. M. Milligan & J. F. Wilkinson, *British Medical Journal*, 2, 477-481, 16/10/43

This preliminary report from the Department of Clinical Investigation and Research, *Manchester Royal Infirmary* and the Public Health Department, Glossop, summarizes the results of an investigation covering 37 weeks between October 1941 and July 1942 on 400 school-children in Glossop between the ages of 9 and 14 years. All the children lived at home but had certain meals at school. They were divided into two groups. The "vitamin group" received 5 daily doses per week of 4,000 international units of vitamin A, 350 international units of "vitamin B complex," 1,000 international units of vitamin C, 600 international units of vitamin D, 2 mg. of riboflavin and 20 mg. of nicotinamide. The "control group" was given capsules containing no vitamins.

In a study of the vitamin-C levels of the children, the ascorbic-acid-saturation test formulated by Harris & Abbasy (1937) was used, and in some cases the ascorbic acid in whole

blood was determined by the method of van Eekelen, Emmerie & Wolff (1937), which involves clearance with mercuric acetate and reduction of dehydroascorbic acid by H₂S. Three months after the beginning of the investigation, by which time the "vitamin group" had each taken an average of 3,000 mg. of ascorbic acid, all the 400 children were given two test doses of ascorbic acid (11 mg. per kg. body weight). All the "vitamin group," but only 28% of the "control group," were saturated. From April to June of the same year (1941) the vitamin-C intake in the diet was assessed as under 15 mg. per day in 40% and between 15 and 30 mg. per day in 35% of all children. The vitamin-C nutrition varied according to social standard but a relatively large amount of severe deficiency was found. Glossop children are said to compare very badly with school-children in other areas.

The incidence and degree of vitamin-A deficiency in the children was assessed by the methods described by Yudkin (1941); a threshold lability of 0.5 log unit or over was accepted as definite evidence of deficiency of vitamin A. On this basis, 16% of the children were deficient, 7% probably deficient and 15% possibly deficient. The daily dietary intake of vitamin A was assessed as over 50 international units per kg. body weight in nearly half the children; 20-30 international units per kg. in another 20%; and less than 20 international units per kg. in 7%. It was tentatively suggested that a dietary intake of over 30 international units per kg. can be described as the minimal daily requirement for children aged 9-14 years.

In the third part of the investigation as reported, five small groups of from 20-50 boys were selected for certain special tests, carried out over a period of 36.7 weeks, the results of which were analysed statistically. The diets of all these boys were carefully investigated and it was believed that the groups differed only in regard to their vitamin intakes; certainly there were no significant differences between the groups in age. Although there were no significant differences in percentage gains in height, a group of 20 vitamin-A deficient boys gained significantly less in weight than a group of 36 boys from the "vitamin group." In an endurance test involving the length of time that the subjects could hold themselves suspended from a horizontal bar, the performance of groups of boys deficient in vitamin A and in vitamins A and C significantly deteriorated during 36.7 weeks, and there was a significant difference between these groups and boys from the "vitamin group." No significant differences between groups were detected in strength (arm dynamometer) or in endurance, and saturation of C-deficient boys with ascorbic acid produced no improvement in their physical efficiency as determined in this way. It was concluded therefore that the short-term effects of ascorbic acid appear to be different from its long-term effects. Examination of groups of boys showed no significant difference in the incidence of gingivitis between C-deficient and "vitamin group," but the incidence of infection was significantly lower in a "vitamin group" than in both A-deficient and C-deficient boys. It was also considered at the end of the investigation that children of the "vitamin group" had "clearer, smoother and sleeker" skins than were found in other groups.

No significant differences between groups were found in respect of plasma phosphatase values (method of King, Haslewood & Delory, 1937) or serum complement titres (method of Ecker, Pillemer, Wertheimer & Gradis, 1938).

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536

THE EFFECT OF SUPPLEMENTS OF VITAMINS AND MINERALS ON THE HEALTH OF GIRLS

by H. Fowke, *British Medical Journal*, 2, 519, 23/10/43

The investigation of which this paper forms a preliminary report was made between February 1941 and April 1942 under the direction of the Ministries of Food and Health. 214 girls between the ages of 8 and 12 years distributed between five institutions in the North of England were

divided into two approximately equal groups, one of which was given a daily ration of 1 ounce [about 28 g.] of "fortified chocolate" containing 2,000 international units of vitamin A, 250 international units of vitamin B₁, 100 international units of vitamin D, 35 mg. of vitamin C, 250 mg. of calcium and 10 mg. of iron. The control group of girls received similar chocolate to which nothing had been added. The dietary conditions in the different institutions varied and there was a general improvement in all diets, as assessed from tables, during the experimental period. Calculation of the calorie values and contents of animal protein, calcium, iron and vitamins A, B₁ and C, before the experiment began and again seven months later, showed that in two of the institutions the diets were deficient in all nutrients, marginal in two others, and probably adequate in the fifth. At the beginning of the investigation, after six months, and at the end of a year, a complete medical examination was made of each child. Data on the following points were obtained; height, weight, sitting height, chest-circumference, the time the breath could be held, the lifting-power measured by a spring dynamometer, the time each child could hang from a horizontal bar. No statistically significant differences were found between the two groups in respect of any of these functions. This may have been due to a steady improvement in the basic diet during the investigation or to the fact that the tests used were insufficiently sensitive to detect minor degrees of malnutrition.

The investigation established that chocolate is a most satisfactory medium for the incorporation of vitamins and minerals. It is a food in itself, with a popular appeal and a pleasant taste strong enough to conceal that of the supplements. Tests of the keeping qualities of vitamins A, B₁ and C in specimens of chocolate stored at room-temperature for four months showed remarkable stability.

537

THE INFLUENCE OF SUPPLEMENTS OF VITAMINS A, B₁, B₂, C, AND D ON GROWTH, HEALTH, AND PHYSICAL FITNESS

by E. R. Bransby, J. W. Hunter, H. E. Magee, E. H. M. Milligan & T. S. Rodgers, *British Medical Journal*, 1, 77-78, 15/1/44

This paper contains a summary of the results of an investigation carried out in 1941-42 on approximately 1,400 school-children and adults in order to determine whether growth, health and physical fitness could be improved by the addition to the diet of supplements of synthetic vitamins. The vitamin capsules employed were a gift to the Ministry of Health from a group of physicians in the United States and had the following composition: Vitamin A 4,000 international units, thiamin 333 international units, riboflavin 2 mg., ascorbic acid 1,000 international units, nicotinamide 20 mg., and vitamin D 600 international units. The vitamin content of the capsules was checked by the *Medical Research Council* four times during the tests.

Three of the five tests carried out were performed on 1,242 elementary school-children in Ipswich, Glossop and London, between November-December 1941 and July-August 1942. The children were examined before, during and after the administration of vitamin supplements and were divided at random into two equal groups, one of which received a capsule every school day and the other a control capsule of arachis oil. It was found that the administration of the capsules had no significant effect on rate of growth, nutritional status, muscular strength, condition of teeth and gums, or absence from school on account of illness.

The remaining tests were done on 214 adult male factory workers and were carried out over the same period and on the same general lines. The vitamin capsules were observed to have no significant effects on weight, hæmoglobin, blood-pressure, absence through illness, or output of work.

538

GROWTH AT HOME AND AT SCHOOL

by E. M. Widdowson & R. A. McCance, *Lancet*, 2, 152-153, 29/7/44

It has previously been reported by Allan (1937, 1939) that boys at "public schools" * in England gain weight more

* [a term used in Britain to denote the larger private schools, most of which are well endowed and of ancient foundation. Most pupils at these schools are residential.]

rapidly during the holidays than they do during the term. This paper from the Department of Medicine at Cambridge contains an analysis of the gains in weight and height of groups of boys in their thirteenth, fourteenth and fifteenth years in three well-known public schools. The boys were weighed and measured at the beginning and end of each term between 1938 and 1943, and the monthly increments of weight and height were calculated for each boy for three terms and three holiday periods. The mean results for all the boys were then compared.

In two schools out of three, the average monthly gains both in height and weight of 930 boys were invariably greater during the holidays than they were during the terms. During the 17 weeks of holidays these boys gained about twice as much weight as they did during the 35 weeks of term, but the increases in height were not so striking. At the third school (240 boys), the boys grew more regularly throughout the year and the most rapid gains tended to take place at school.

The authors point out that this irregular growth can hardly be attributed to a normal physiological mechanism. It may be that the greater mental and physical strain at school accounts for the diminished growth-rate: there was no reason to suppose, however, that conditions in the third school were any different from those in the other two, and the boys came from the same type of home. The authors feel that "it is difficult to get away from the view that the differences in growth-rate must ultimately be nutritional in origin." They conclude that "until we know more about the causes and consequences of these irregularities of growth, results such as these emphasize how necessary it is for boys to have good holidays, at home, free so far as possible from work, camps and all other kinds of forced labour."

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539

THE NUTRITIONAL STATUS OF CAMBRIDGE SCHOOL-CHILDREN

by J. Yudkin, *British Medical Journal*, 2, 201-205, 12/8/44

This paper by Dr. John Yudkin, who formerly worked at the *Dunn* Nutritional Laboratory, Cambridge, contains the results of a survey of over 1,100 Cambridge children between the ages of 4 and 11 attending elementary schools. This represents nearly 20% of this age-group in the area. The nutritional status of the children was assessed in January and February 1942 and again in the same months in 1943. The results were found to compare favourably with those reported from other parts of the country. Compared with children in a better-class area, children from poor quarters of the area were on the average 0.8 in. [about 2 cm.] shorter, 2.6 pounds [about 1.3 kg.] lighter, had 2% less hæmoglobin, a grip about 1.25 kg. weaker and showed more changes in conjunctival epithelium when examined with the slit-lamp microscope (Kodicek & Yudkin, 1942). At the second examination, a year later, the heights and weights were slightly greater than for children of the same age examined the year before. It may be said, therefore, that there had been no deterioration in their diets between the third and fourth years of the war.

Further studies were later made on about 200 of the oldest children to determine whether "physiological performance" can be improved by the giving of vitamin supplements (for the results of this investigation see Jenkins & Yudkin, 1943). After the first examination, half the children at each school were given, each day, a pellet containing vitamin A 5,000 international units, vitamin B₁ 1 mg., vitamin C 25 mg., and vitamin D 500 international units, and the other half received dummy pellets. Allowing for holidays and absences from school, the pellets supplied approximately half the daily requirements of vitamins A, B₁, C and D. After a year no effect was found in the gains in height and weight, hæmoglobin, strength of grip, dark-adaptation, resting pulse rate, vital capacity, breath-holding time or endurance as measured by the R.A.F. mercury test. There was, however, an improvement in vitamin-C saturation, a decrease in the incidence and duration of colds, and an improvement in school behaviour as assessed by the teachers. The author points out that "the absence of effect on growth, hæmoglobin,

etc., cannot be taken to imply that these are not limited by nutritional factors."

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¹ [see BMB 534] ² [see BMB 33]

540

THE NUTRITIONAL STATUS OF CHILDREN AND MOTHERS OF INDUSTRIAL TOWNS

by J. Yudkin, *Medical Officer*, 72, 93-94 & 101-102, 16/9/44 & 23/9/44

The author has previously reported (Yudkin, 1944) a nutritional investigation in Cambridge school-children. In the present paper he describes a more limited investigation on working-class mothers and children of 66 families from Aberdeen, Dundee, and Glasgow.

On the average, these children from industrial towns were nearly 1½ inches [about 3.5 cm.] shorter, weighed 4 pounds [about 1.8 kg.] less, had a hæmoglobin level 4% lower, and a strength of hand-grip 1½ kg. less than the Cambridge school-children. There was a correlation between the financial state of the family and the nutritional state (as judged by the tests described) of its members.

Although the best use was not always made of the income available for food, the author states that there was not in most cases sufficient money for an adequate diet. The data from this survey are summarized in 9 tables and 3 graphs.

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¹ [see BMB 539]

541

NUTRITION AND SCHOLASTIC ATTAINMENT

by I. F. MacKenzie, *British Medical Journal*, 2, 205-207, 12/8/44

With the ultimate object of promoting education, the Education (Provision of Meals) Act was passed in 1906, granting local authorities powers to provide meals for children attending public elementary schools. Even to-day, however, defective nutrition is common, and the question arises whether malnutrition interferes with the educational progress of the child. Such evidence as at present exists suggests that there is a correlation between physical condition and mental development (Sandwick, 1920; Baldwin, 1922; Pearson, 1923; Habakkuk, 1926; Mann, 1926; Leighton & Clark, 1929; Dawson, 1931).

The author of this paper, who is Deputy County Medical Officer for Herefordshire, has examined the nutritional status of 712 children between the ages of 8 and 14 attending a group of public elementary schools. The assessment of nutrition was made on the findings of a clinical examination which followed that recommended by the League of Nations Health Organization (1938), and the classification used was that sponsored by the Board of Education (1934). The pupils were chosen by the teachers to represent the "bright" and the "slow" in comparison with the class averages. Of the bright children, 28.2% were graded Nutrition A and 5.6% Nutrition C. Only 6.7% of the slow children were grade A, while 22.1% were graded C. From a comparison of the results in 280 boys and 303 girls it was concluded that the mental activity of girls is even more closely related to their general physical state than is that of boys.

The author holds the view that "subnormal nutrition can constitute a serious handicap to the educational advancement of a child" and believes that a malnourished child may, as the result of proper feeding, "attain to an ability to use his mental powers equivalent to that enjoyed by his better-nourished school-mate."

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542

NUTRITION AND SIZE OF FAMILY

by J. Yudkin, *Lancet*, 2, 384-387, 16/9/44

The author reports the results of comparative tests of physical condition in school-children from large and small families of (a) a poor quarter and (b) a more prosperous area of Cambridge. The height, weight, hæmoglobin levels, and muscular strength (hand-grip) of children from larger families in the poor area were significantly lower than those of children from small families. The differences between children of large and small families in the more prosperous area were smaller (taking into consideration the smaller disparity in size of family in this group).

The author concludes (i) that family income in the poor area is not sufficient to secure physical development for more than a limited number of children; (ii) that family allowances are necessary to improve the nutritional status of children of large families.

543

ACCELERATION OF CO-ORDINATED MUSCULAR EFFORT BY NICOTINAMIDE: Preliminary Report to the Medical Research Council

by I. M. Frankau, *British Medical Journal*, 2, 601-603, 13/11/43

This communication summarizes the results of a series of experiments undertaken to show by means of a selected test the effect, if any, of certain vitamins on the physical efficiency and the fatigability of healthy young males. Preliminary experiments demonstrated that the usual agility-test was not adequate to produce any measurable degree of fatigue in the subjects, who were drawn from the personnel of the *Royal Air Force*. The test finally adopted consisted of running rapidly for about 300 yards, bending and turning quickly and dropping discs accurately on a closely fitting shaft. No undue stress was laid upon speed or accuracy, but the need to finish with maximal exertion was emphasized.

Two control tests were recorded on one day at intervals of 30 minutes, and two "experimental" tests with an interval of 15 minutes on another day. No significant change was detected after ingesting on three successive days vitamin tablets containing vitamin A, 8,000 international units; vitamin D, 1,200 international units; aneurin, 2 mg.; riboflavin, 4 mg.; ascorbic acid, 100 mg.; and nicotinamide, 40 mg.

After 4 days' dosage with vitamin tablets which provided aneurin 5 mg., riboflavin 5 mg., ascorbic acid 100 mg. and nicotinamide 50 mg. per day, tests carried out on the fifth day showed a significant improvement in this group over the control group, both as regards co-ordination and endurance. Further experiments omitting aneurin and both aneurin and ascorbic acid showed that neither of these two substances was required to produce this effect.

Subsequently, experiments were carried out on the effect of nicotinamide alone. Control times were recorded on one day. On the following day each subject received 50 mg. of nicotinamide, and the test was repeated on one group after 1½ to 2½ hours and on a second group 5½ to 6½ hours later. Yet another group was given 200 mg. 1½ to 3 hours before the test. A significant improvement was observed in all subjects after nicotinamide, and the results were more evident at short intervals after the dose. Administration of nicotinamide for 6 successive days followed by tests on the seventh demonstrated the same general trend.

Diet and Disease: Communal Feeding

544

NUTRITIONAL DEFICIENCY IN THE PATHOGENESIS OF DISEASE

by J. Yudkin, *British Medical Journal*, 1, 5-7, 1/1/44

Dr. Yudkin, formerly *Sir Halley Stewart Research Fellow* at the *Dunn Nutritional Laboratory*, Cambridge, points out in this paper that certain criteria are necessary for assessing the

part played by nutritional deficiency in producing obscure signs and symptoms or syndromes of uncertain aetiology. These criteria are analogous to Koch's postulates and fall into three groups.

Criterion 1. It should be possible to demonstrate the existence of a deficiency of the nutrient. Evidence of such deficiency may be found at any point between the nutrient in the diet and its utilization in the tissues. A careful dietary history is therefore essential. Under this head are included such factors as income level, season, habitat, special dietary régimes, conditions of employment, standard of preparation and cooking of the food, etc. Evidence of defective absorption must next be considered and thirdly the possibility of increased utilization, such as occurs, for example, in pregnancy or as the result of fever or heavy manual work. Specific signs of deficiency disease may be obtained from clinical examination, and as the result of functional tests and/or laboratory investigations of blood and urine. Unfortunately, however, these methods have often been used uncritically; though superficially simple they require rigid control and careful interpretation.

Criterion 2. Deficiency of the nutrient should result in the production of the disease. This test may be applied in experimental animals, in which case the results must be evaluated with due care, or in human beings. Conflicting results are often obtained in human tests by different workers, possibly as the result of an inadequate number of subjects, individual variations in behaviour and requirement, and differences in the composition of the diet.

Criterion 3. The disease should be cured by replacement of the deficient nutrient. In assessing the value of a therapeutic test, however, it is important to allow for the possibilities (a) of spontaneous remission and conversely (b) that the pathological process may have progressed to an irremediable stage. The existence of multiple deficiencies is a less well recognized reason for failing to obtain improvement. Lastly, when a positive effect is finally obtained by the use of a vitamin supplement it is not always legitimate to assume that the existence of a deficiency has thereby been proved.

545

EFFECTS ON RATS OF PROLONGED FEEDING WITH THE STAPLE AFRICAN DIET

by J. Gillman, *British Medical Journal*, 1, 149-150, 29/1/44

It is known that pulmonary tuberculosis and other diseases of the respiratory tract are prevalent among South African negroes, in whom cirrhosis of the liver, and especially primary cancer of the liver, are encountered with unusual frequency. Malnutrition is widespread among the Africans, whose staple diet consists largely of maize meal and sour milk. This paper from the Department of Anatomy of the University of Witwatersrand, Johannesburg, represents the collaborative efforts of many workers in the Department who have investigated the effect of such a diet on normal rats. Full post-mortem examinations were made of 12 rats who had received liberal amounts of the diet for 14 months.

In all the animals, pronounced disease of the liver was evident macroscopically. This varied from diffuse enlargement of the whole liver with obvious fatty change to a widespread nodular cirrhosis often involving especially the left lobe. The hearts were grossly enlarged, fat deposition in the mesentery, retroperitoneal and subcutaneous areas was unusually abundant, and in 9 animals one or both lungs showed inflammatory lesions with bronchiectasis or abscess formation. Pathological changes were also found in the skull, teeth, pituitary, thyroid, suprarenals and alimentary tract. These striking abnormalities were present without any recognizable manifestation of acute vitamin-deficiency disease. No lesions of the liver of the kind described were ever observed in many thousands of rats examined post mortem over a number of years.

The author rightly points out that "the production of liver damage by means of a diet which forms the staple of the overwhelming number of Africans in South Africa is not without its sociological implications." Further work is in progress to determine the factors responsible for these remarkable changes.

546

SOME PROBLEMS OF COMMUNAL FEEDING

by C. P. Stewart, *Edinburgh Medical Journal*, 51, 215-228, May 1944

This is the text of a *Honyman Gillespie* lecture given in the Royal Infirmary, Edinburgh. The author points out "that the part played by communal feeding in the nutrition of our people is a very considerable one, and that a large fraction of the population depends upon it for the whole or part of its food." Community feeding provides an excellent field for research but the problems differ somewhat between the "closed" community (hospital, boarding-school, hostel, etc.) and the canteen and workers' restaurant. In both, however, there is the same need for a nutritional standard high enough to be of educational value, for variety, palatability and attractiveness in the food, for cooking and serving methods which will preserve the labile vitamins, and for economy without sacrifice of true value.

The author describes the results of a survey made in a boarding-school for boys aged 9 to 12 years, comparing his results with standards taken from the Report of the Hot Springs Conference and showing how closely practice may approximate to precept even with the food restrictions of war-time. A good diet, however, must satisfy other criteria than those of chemical analysis, and the boys' diet is further considered as to its variety, palatability and attractiveness. Cooking and serving cannot be assessed quantitatively, but objective evidence can be obtained on these points by determinations of the ascorbic acid content of the food as eaten. Figures are quoted for potato and cabbage for the school and *British Restaurants* (public restaurants instituted by the Ministry of Food) which reveal the better cooking and serving in the former and the great variation in the latter.

Dr. Stewart then discusses hospital diets, and shows that in many respects these must often be regarded as unsatisfactory. He found that patients in hospital were obtaining from 300 to as much as 1200 calories per day from food brought in by their friends.

Finally, the standards to be adopted for the "midday" (or "midnight") meal in the factory canteen are discussed and it is shown how these may require to be adjusted according to habit, type of employment and local conditions.

547

THE MIDDAY SCHOOL MEAL: A STUDY OF ITS RELATION TO THE TOTAL WEEKLY DIETARY OF A GROUP OF SCHOOLBOYS

by R. P. Cook, W. A. Davidson, D. M. Keay & D. G. McIntosh, *British Medical Journal*, 2, 443, 30/9/44

This is a brief report of an investigation intended to show what proportion of the total intake of important nutrients was provided by the midday school meal of a group of 39 boys of 14-15 years who agreed to co-operate. Each boy recorded on a tabular sheet, which was provided, his food-intake at each meal for one week. Foodstuffs were divided into 20 categories, and their content of the nutrients considered was calculated from tables.

The mean percentage of the intake of calories obtained from the school-meal was 35.68. The corresponding figures for important nutrients were: total protein, 35.92; "first-class protein," 44.4; vitamin A, 67.8; vitamin B₁, 37.13; ascorbic acid, 57.8; calcium, 42.3; available iron, 37.17. The authors regard the school meal as providing a valuable contribution to the dietary which would probably have been inferior if all meals had been taken at home.

BOOKS, MEMORANDA, REPORTS

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548/83

SULPHONAMIDES IN THE TREATMENT OF MENINGOCOCCAL MENINGITIS

Report to the Scientific Advisory Committee, Department of Health for Scotland. Edinburgh, H.M. Stationery Office, 1944. 20 pages. 4d. [£0.016]

During the early part of 1940, an exceptionally large epidemic of meningococcal meningitis, while giving rise to some anxiety, also gave an opportunity of a detailed assessment of the value of drugs of the sulphonamide group in the treatment of this infection. This report evaluates the relative efficiency of the various sulphonamides used. Certain hospitals were selected for the enquiry, and the report includes an analysis of all cases accepted by these hospitals between 1936 and 1941. As sulphonamides were little used before 1938, a comparison is possible with the results of treatment in pre-sulphonamide days. The records of 2,223 cases of meningococcal meningitis are analysed and it is shown that the use of sulphonamide drugs has caused a marked reduction in the fatality-rate (16.7% as compared with 52% in those receiving serum alone). Mortality was found to be closely associated with age, maximal rates occurring under 2 years and over 35 years. The method of treatment was as follows: no serum or drug, 12 cases; serum or antitoxin, 199; sulphanilamide, 128; sulphapyridine, 1,468; sulphathiazole, 75; miscellaneous sulphonamides, 91; serum or antitoxin and sulphonamides, 250. Comparison between sulphanilamide, sulphapyridine and sulphathiazole does not suggest that any one possesses clear advantages over the others. Between 70% and 80% of cases receiving sulphonamides were clinically cured within 4 weeks. The dosage given varied widely in individual cases and the analysis does not permit a dogmatic statement with regard to optimum dosage. The sulphonamides appear to be equally effective when given during any part of the first week of illness, although the prompt institution of treatment is important. Various complications were encountered; the importance of pneumonia as a cause of death is emphasized.

548/84

MEDICAL DISEASES OF WAR

by Sir Arthur Hurst. 4th edition. London, Edward Arnold & Co., 1944. 511 pages; 48 illustrations. £1 1s. [£1.05]

This book originated during the 1914-18 war as a review of experience gained on active service on both western and eastern fronts. At the beginning of the present war it was one of the best available authorities on those medical diseases which become prominent, both among soldiers and civilians, in time of war. In 1940 appeared the first edition of the book in its present form, a modern, extensively revised version of the original work. This new book, which has reached its fourth edition in four years, reflects the wide reading and vast experience of the author. In its construction he has had the co-operation of several authorities. Particularly important is the section on the functional nervous diseases. In the present edition, the chapter on epidemic jaundice and infective hepatitis and the sections on sciatica and the treatment of bacillary dysentery have been rewritten. The section on the seborrhœic state has been replaced by one on dermatophytosis. Major alterations have been made in the sections on digestive disorders, malaria, tetanus, and the hysterical sequelæ of concussion, and minor corrections and additions are evident throughout the remainder of the work. The recent death of the author of this work is a great loss to British medicine.

Chapter headings: (i) predisposing causes of war neuroses; (ii) hysterical symptoms in soldiers; (iii) hysterical paralysis; (iv) hysterical contractures; (v) rheumatism, sciatica, and hysterical postures and gait; (vi) hysterical tremor; (vii) hysterical fits; (viii) disorders of speech; (ix) functional disorders of hearing; (x) functional disorders of vision; (xi) hysterical stupor and amnesia; (xii) cerebral and spinal concussion; (xiii) exhaustion resulting in neurasthenia; (xiv) hyperadrenalism and hyperthyroidism; (xv) anxiety neuroses of war (by T. A. Ross); (xvi) digestive disorders in soldiers; (xvii) effort syndrome; (xviii) trench fever; (xix) louse-borne typhus fever (by Melville D. Mackenzie); (xx) typhoid and paratyphoid fevers; (xxi) dysentery; (xxii) epidemic jaundice; infective hepatitis; (xxiii) malaria (by H. B. F. Dixon); (xxiv) meningococcal fever (by A. W. Stott); (xxv) diphtheria (by E. H. R. Harries); (xxvi) tetanus; (xxvii) war nephritis; (xxviii) skin disease in war (by H. W. Barber); (xxix) gas poisoning.

548/85

LECTURES ON DISEASES OF CHILDREN

by Sir Robert Hutchison & Alan Moncrieff. 9th edition. London, Edward Arnold & Co., 1944. 478 pages; 108 illustrations. £1 1s. [£1.05]

It is 40 years since this book first appeared, having originally consisted of lectures delivered by Sir Robert Hutchison in a sys-

tematic course at the London Hospital, of which he is Consulting Physician. This ninth edition is the responsibility of Dr. Alan Moncrieff, Physician to the Children's Department of the Middlesex Hospital and to Out-patients, *Hospital for Sick Children*, London. The book, written in didactic style, is essentially practical and clinical in its approach to the subject; detailed reference to treatment is a prominent feature. In this new revision, the principal alterations are to be found in the sections dealing with infection in the newborn, the treatment of infantile diarrhoea, the cause and treatment of celiac disease, the treatment of threadworms, and the types of congenital heart disease, and sections on the Rh factor and on encephalitis have been added. This book is a standard British work on pædiatrics.

Chapter headings: (i) the clinical examination of sick children; (ii) infant feeding—breast-feeding; (iii) infant feeding—artificial feeding; (iv) some diseases of the newly-born; (v) the premature infant; (vi) diet after the period of infancy; (vii) the digestive disorders of infancy—colic and vomiting; (viii) congenital pyloric stenosis; (ix) infantile diarrhoea; (x) celiac disease; (xi) chronic constipation in infancy and childhood; (xii) wasting; (xiii) congenital syphilis; (xiv) tuberculosis in childhood; (xv) rickets; (xvi) infantile scurvy and pink disease; (xvii) the dyspepsias of childhood; (xviii) rheumatism in childhood; (xix) acute rheumatic carditis; (xx) some disorders of the heart in childhood; (xxi-xxiv) the respiratory diseases of children; (xxv) some behaviour problems in childhood; (xxvi) some functional nervous diseases of childhood; (xxvii) convulsions in childhood; (xxviii) the paralyses of childhood; (xxix) meningitis and encephalitis; (xxx) on mental deficiency in childhood; (xxxi) the blood disorders of early life; (xxxii) chronic splenomegaly in childhood; (xxxiii) some common affections of the genito-urinary system in childhood; (xxxiv) affections of the liver in childhood; (xxxv) some common symptoms of disease in children and their diagnostic significance; (xxxvi) the diagnostic significance of abdominal pain in childhood; (xxxvii) fever of obscure origin; (xxxviii) some of the commoner skin diseases of infancy and childhood; (xxxix) disorders of growth and development.

548/86

AN INTRODUCTION TO PHYSICAL METHODS OF TREATMENT IN PSYCHIATRY

by W. Sargent & E. Slater. Edinburgh, E. & S. Livingstone, Ltd., 1944. 171 pages. 8s. 6d. [£0.425]

Increasing knowledge of the aetiology of mental disease has resulted in a shifting of emphasis from psychogenetic to physical interpretations. Symptoms once thought to be of exclusively psychogenic origin have now been found to rest on an underlying physical deviation from the normal. The past decade has seen important advances in somatic methods of treatment in psychiatry (although they are still admittedly empirical), and this book, whose joint authors are medical officers to the *Maudsley Hospital*, London, provides a valuable and timely introduction to the subject. It is not a complete text-book, but will give a balanced view of the scope of physical methods of treatment. The writers, who have had special opportunities of applying these methods in the treatment of civilian and military psychiatric casualties and therefore write with authority, consider that it contains sufficient material to provide a basis for active treatment in the psychiatric ward of a general hospital or in the reception and treatment wards of a mental hospital.

The chapter headings are: (i) the insulin treatment of schizophrenia; (ii) modified insulin therapy; (iii) convulsion therapy; (iv) the treatment of cerebral dysrhythmia (bromides, luminal, epanutin, benzedrine); (v) chemical sedation and stimulation; (vi) continuous sleep treatment; (vii) some special uses of intravenous barbiturates; (viii) diet, vitamins and endocrines; (ix) prefrontal leucotomy; (x) the malarial treatment of general paralysis; (xi) the relation of psychological to somatic treatment.

An important literature has grown up around this subject, and the authors would still further increase the value of this book by the addition, in subsequent editions, of a bibliography of the more pertinent references.

548/87

HOUSING MANUAL 1944

Prepared by the Ministry of Health and the Ministry of Works. London, H.M. Stationery Office, 1944. 103 pages; 102 plans and photographs. 2s. [£0.1]

This Manual has been compiled with the object of giving technical guidance to local authorities, architects, builders, manufacturers

and others, on the lay-out, planning and construction of permanent houses to be built under the Government's short-term programme covering the first two years after the end of the war in Europe. Local authorities are expected to prepare their own plans in the light of the technical guidance given by this publication.

In July 1944 the Design of Dwellings Sub-Committee of the Central Housing Advisory Committee (appointed by the Ministry of Health) presented its report, and its recommendations have in general been adopted in the Housing Manual. There is detailed discussion of (i) housing and site planning; (ii) the house and its surroundings; (iii) the three-bedroom house; (iv) some special occupants—rural workers, old people, single persons, etc.; (v) flats; (vi) efficiency in building; (vii) new materials and methods; (viii) the heat installation; (ix) services and equipment; there are in addition appendices on space standards and structural standards. The arrangements for cooking meals usually determine the "way of living" in the working-class house and the plans provided have been evolved from this way of living. These arrangements for cooking will also indicate the fuel or fuels to be used and, to a large extent, the nature and arrangement of the fuel-burning installations and appliances.

One of the major improvements in the lay-out of sites during the past 25 years has been the use of more open forms of development as compared with the close development associated with working-class districts and industrial centres during the nineteenth century. While the plans proposed take into account the value of light and air thus obtained, the establishment of self-contained units or units properly linked to existing communities is envisaged, in order that the tendency to unregulated spreading of sites shall be counteracted. It is urged that provision be made for schools, shopping centres, open spaces, etc., at the outset.

Advice on fuels and appliances has been contributed by the Ministry of Fuel and Power, and the Ministry of Town and Country Planning has advised on site planning and lay-out. The Manual includes many diagrams illustrating different types of plans and drawings of fittings and equipment. A number of excellent photographs of houses already built by local authorities illustrate various arrangements in style.

The Manual is itself an excellent production, set in clear type with carefully drawn plans and excellent half-tone illustrations. A good index is provided.

548/88

A TEXT-BOOK OF PSYCHIATRY

For Students and Practitioners

by D. K. Henderson & R. D. Gillespie. Sixth edition. London, Humphrey Milford, Oxford University Press, 1944. 719 pages. £1 5s. [£1.25]

This book is dedicated to Adolf Meyer, and in general it reflects the biological interpretation of mental disease associated with Meyer and the North American school, while giving due attention to the work of the continental psychiatrists. Dr. Henderson is Professor of Psychiatry in the University of Edinburgh and Dr. Gillespie is Physician for Psychological Medicine at Guy's Hospital. This is an excellent publication and is deservedly recognized as the standard British text-book on psychiatry. Its scope is shown by its chapter headings: (i) historical review of the care and treatment of mental illness; (ii) classification; (iii) aetiology; (iv) method of examination; (v) symptomatology; (vi) general psychopathology; (vii) psychoneurotic reaction-types; (viii-ix) affective reaction-types; (x) schizophrenic reaction-types; (xi) paranoia, paraphrenia and paranoid reaction-types; (xii) psychopathic states; (xiii) special methods of physical treatment; (xiv) the organic reaction-types; (xv) epilepsy; (xvi) mental defect; (xvii) psychoses and psychoneuroses in war; (xviii) the psychiatry of childhood; (xix) occupational therapy; (xx) relations of psychiatry and law.

In the new edition the authors have taken account of the increasing incidence of the psychoneurotic forms of reaction; a special chapter on physical methods of treatment records the great advances made in these methods during the past few years, and carefully examines the results obtained by their use; the discussion on epilepsy has been amplified; in the light of their experience the authors have now modified Kraepelin's classification of the schizophrenic states, the paranoid states being removed from the group; the social aspects of psychiatry, to which increasing importance is likely to accrue in the future, receive additional commentary in appropriate places throughout the text. There is a wealth of illustrative case-histories, a short bibliography, and numerous references to the literature appear throughout the book. It would perhaps be an advantage to gather these references together, and to incorporate them into a comprehensive bibliography of the subject, to form an important additional section to this invaluable book.

549

GUIDE TO THE JOURNALS

Annals of the Rheumatic Diseases

4 : September 1944

- The nodules and lymph-gland enlargement in rheumatoid arthritis: also a syndrome of rheumatoid arthritis combined with multiple xanthomatous connective tissue infiltrations. (F. P. Weber) 3-10
Observations on the natural history of acute rheumatic fever. (W. S. C. Cope-man) 11-21
Aspects of "fibrositis." (F. A. Elliott) 22-25
A case of tuberculous rheumatism (Grocco-Poncet type). (E. Montuschi) 26-28

Biochemical Journal

38 : 1944

PARTIAL INDEX

- The riboflavin content of food served in Royal Air Force messes. (T. F. Macrae, E. C. Barton-Wright & A. M. Copping) 132-135
The fluorimetric estimation of 3:4-benzpyrene in whole mice. (H. Weil-Malherbe) 135-141
A note on the fluorimetric estimation of 3:4-benzpyrene by the method of Miller and Baumann. (H. Weil-Malherbe) 141
Chemistry of tissues. 1. Chondroitin from cartilage. (H. G. Bray, J. E. Gregory & M. Stacey) 142-146
Quenching effect of electrolytes on the fluorescence intensity of riboflavin and thiochrome. (P. Ellinger & M. Holden) 147-150
A method for the estimation of nicotinamide methochloride in urine. (R. A. Coulson, P. Ellinger & M. Holden) 150-154
Enzyme formation and polysaccharide synthesis by bacteria. 2. Polysaccharide formation by *Rhizobium radicicola* strains. (H. G. Bray, E. Schlüchterer & M. Stacey) 154-156
The 'Q' notation for expressing metabolic activities in tissue slices. A critical study. (S. J. Bach) 156-159
Combination of potato virus X and tobacco mosaic virus with pepsin and trypsin. (A. Kleczkowski) 160-167
The nature of *Aeromonas* fermentation. (R. Y. Stanier & G. A. Adams) 168-171
Diplococcin, an anti-bacterial protein elaborated by certain milk streptococci. (A. E. Oxford) 178-182
Biochemical characterization of the actions of chemotherapeutic agents. 2. A reaction of hemolytic streptococci, involving pantothenate-usage, inhibited by pantoyltaurine, and associated with carbohydrate metabolism. (H. McIlwain & D. E. Hughes) 187-195
A quantitative micro-method for the separation of inorganic arsenite from arsenate in blood and urine. (T. B. B. Crawford & I. D. E. Storey) 195-198
Glycogen. 9. The magnitude of the 'unit chains' of liver glycogen of rabbits supplied with glucose, fructose and sucrose. (J. S. D. Bacon, E. Baldwin & D. J. Bell) 198-201

British Heart Journal

6 : July, 1944

- Myocardial infarction. (T. E. Lowe & W. B. Wartman) 115-128
Acute left auricular failure. (C. Bramwell & A. M. Jones) 129-134
Cardiac involvement in spirochætal jaundice. (W. E. Hume & P. Szekely) 135-138
Incomplete bundle branch block. (C. W. C. Bain) 139-148
The place of foliandrin within the group of cardiac glucosides. (L. E. Schindler & K. Braun) 149-153
Temporal arteritis. (J. W. Brown & F. Hampson) 154-156
Nicotinic acid in the treatment of angina pectoris. (W. Stokes) 157-160
Pulmonary embolism: the clinical and cardiographic progress of a case. (D. Lewes) 161-166

British Journal of Dermatology and Syphilis

56 : July-August 1944

- The reticular tissue and the skin. (A. H. T. Robb-Smith) 151-176
Contact dermatitis in a morphine factory. With an account of the occurrence of "morphia rash" in the manufacture of morphine salts from opium. (S. E. Dore, E. W. P. Thomas & G. C. Green) 177-186

British Journal of Experimental Pathology

25 : June 1944

- Experimental streptococcal lesions of the rabbit's eye and their treatment. (J. M. Robson & A. A. B. Scott) 81-90
Tumours of the thyroid produced by 2-acetyl-amino-fluorene and allyl-thiourea. (F. Bielschowsky) 90-95
The difference in carcinogenicity between shale oil and shale. (I. Berenblum & R. Schoental) 95-96
The production of penicillinase by organisms of the *subtilis* group. (E. S. Duthie) 96-100
The nature and mode of action of staphylococcus coagulase. (W. Smith & J. H. Hale) 101-110

British Journal of Industrial Medicine

1 : July 1944

- Industrial health research: the work of the Industrial Health Research Board, 1918-44. (R. S. F. Schilling) 145-152
Health hazards of coal-mining. (S. W. Fisher) 153-158
Effect of aluminium and alumina on the lung in grinders of duralumin aeroplane propellers. (D. Hunter, R. Milton, K. M. A. Perry & D. R. Thompson) 159-164
Relative sterility of the hands of certain metal workers. (I. Lominski & G. R. Thomson) 165-167
Physical nature of radiations used in industry. (G. D. Rochester) 168-169
Medical aspects of radiations used in industry. (E. Browning) 170-175
Working capacity after thyroidectomy. (W. L. Scott & J. W. Parks) 176-178
Subcutaneous emphysema due to compressed air. (G. P. B. Whitwell) 179
Brightness, well-being and work. (H. C. Weston) 180-196

British Journal of Ophthalmology

28 : September 1944

- A contribution to the study of anophthalmia with description of a case. (T. Rogalski) 429-440
A study of eighty-four cases of delayed mustard gas keratitis fitted with contact lenses. (I. Mann) 441-447
A note on the rosettes, nature and nomenclature of "glioma retinae." (E. Wolff) 448-450
Virus ophthalmia neonatorum. (A. Sorsby, E. E. Hoffa & E. N. Young) 451-457
Incomplete avulsion of the eye: report of a case. (I. C. Michaelson) 458-460
A gas mask wafer for presbyopia. (W. O. G. Taylor) 461-466

28 : October 1944

- A case of polycythæmia vera—extraction of both lenses: satisfactory result. (J. C. Marshall) 481-486
A case of cornea plana. (C. Cockburn) 486-488
The effects of faradically induced currents upon the extrinsic and intrinsic ocular musculature: a clinical self experiment. (J. H. Young) 488-502

Dynamic factors in the formation and re-absorption of aqueous humour. (J. S. Friedenwald) 503-510
 Mucocele of maxillary antrum. (G. E. Dodds) 510-511
 Retro-bulbar neuritis (five cases) due to paranasal sinusitis. (R. Ford) 511-515
 Reconstruction of the lower lid by Hughes' method. (J. Foster) 515-519
 Congenital ectropion associated with bilateral ptosis: case report. (S. Gordon & B. H. Craggs) 520-521
 Angioma of the retina. (I. C. Michaelson) 522-526

British Journal of Radiology

17: October 1944

X-ray diagnosis in gunshot wounds of the abdominal cavity and its significance in field surgery. (S. A. Reinberg) 291-295
 Four primarily radiological lesions found in traumatic chest cases: a preliminary report. (C. J. Hodson) 296-299
 Linear radium source dose calculators. (L. A. W. Kemp) 300-304
 Osteochondritis of patella. (H. Jungmann) 305-307
 The investigation of sciatica and lumbago: the radiological aspect. (J. F. Brailsford) 308-311
 A case of patent ductus arteriosus associated with multiple pulmonary aneurysms and infective endocarditis. (H. R. Holmes) 312-315
 Localisation of foreign bodies by a radiometric method. (W. H. Hastings) 316-318
 Tomographic appearance of the azygos lobe: with a description of two cases and a report of seven cases. (J. H. Crawford) 319-322

British Journal of Surgery

32: 1944

SPECIAL PENICILLIN ISSUE

Army progress with penicillin. (L. T. Poole) 110-111
 The principles of penicillin treatment. (H. W. Florey & M. A. Jennings) 112-116
 Bacteriological methods in connexion with penicillin treatment. (L. P. Garrod & N. G. Heatley) 117-124
 Application of penicillin to war wounds. (J. S. Jeffrey) 124-129
 The bacteriological examination of wounds treated with penicillin. (S. Thomson) 129-131
 The treatment of flesh wounds by early secondary suture and penicillin. (F. H. Bentley) 132-139
 Early closure of soft tissue wounds with chemotherapeutic agents: a comparative study of sulphanilamide and penicillin. (J. J. M. Brown) 140-143
 Battle casualty fractures in Italy: treatment with penicillin. (J. S. Jeffrey) 144-147
 On the use of penicillin to control infection in open fractures of the femur: interim report. (R. Furlong & J. M. P. Clark) 147-154
 Battle casualty fractures of the femur: treatment with penicillin. (R. J. B. McEwan & J. G. Bickerton) 154-158
 Gas gangrene in Italy: a study of 33 cases treated with penicillin. (J. S. Jeffrey & S. Thomson) 159-167
 Treatment of clostridial infections with penicillin. (E. C. Cutler & W. R. Sandusky) 168-176
 Intraperitoneal penicillin in penetrating wounds of the chest. (W. F. Nicholson & C. R. Stevenson) 176-179
 Penicillin in the treatment of war wounds of the chest. (A. L. d'Abreu, J. W. Litchfield & S. Thomson) 179-198
 Penicillin in head and spinal wounds. (H. Cairns) 199-207
 Observations on the prophylactic use of penicillin in the wounds of aerial warfare. (E. C. Cutler, P. C. Morton & W. R. Sandusky) 207-211
 Penicillin therapy in gonorrhoea: a report of 1000 cases of sulphonamide-resistant gonorrhoea and 100 cases of acute gonorrhoea previously untreated. (J. N. Robinson) 211-214
 Penicillin therapy for syphilis. (C. R. Wise & D. M. Pillsbury) 214-217
 Bibliography on penicillin. 217-224

British Journal of Venereal Diseases

20: September 1944

Haemorrhagic encephalitis and intensive mapharside treatment. (F. L. Lydon) 87-97
 Sulphonamide therapy of gonorrhoea in the male: review of four years' experience. (D. I. Williams, A. J. King & C. S. Nicol) 97-108
 A joint venereal diseases service for three rural or urban districts. (A. N. P. Milner) 108-117
 A procedure for the serological diagnosis of syphilis based on a comparative study of five modern serological tests. (F. M. Berger & G. Denton) 118-123
 Ulcerating granuloma of pudenda—treatment by zinc peroxide paste. (H. M. Hanschell) 123-125

British Medical Journal.

2: 9/9/44

Retinal detachment: a series of 78 cases in the Middle East Force. (H. B. Stellard) 329-333
 Nutritional iron deficiency anaemia in wartime. Part III: The haemoglobin levels of school children and pregnant women in 1944, compared with the levels in 1942 and 1943. (L. S. P. Davidson, G. M. M. Donaldson, S. T. Lindsay & M. H. Roscoe) 333-334
 Industrial problems in the Middle East. (A. M. Critchley & I. H. Flack) 334-337
 A classification of deaths of medico-legal importance. (I. Gordon) 337-339
 Specific serum therapy in typhoid fever. (A. E. Hodgson) 339-340
 Technique of blood examination for malaria parasites. (T. Crawford) 348

2: 16/9/44

Laboratory tests in the diagnosis of liver disease: a report on three procedures. (N. F. MacLagan) 363-365
 Artificial respiration: the need for a greatly increased rate in asphyxia. (P. R. Tingley) 366-367
 Psychiatry in detention. (R. R. Prewer) 368-370
 Proteolysed beef in the treatment of calic disease. (A. C. Adamson & D. Lewes) 370-372
 A fracture-dislocation of the ankle occurring in flying accidents. (T. James) 372-373
 A survey of the haemoglobin levels of the poor classes in Aberdeen. (H. W. Fullerton, M. I. Mair & P. Unsworth) 373-374
 Fractures of the carpal bones. (H. A. Harris) 381

2: 23/9/44

Influence of synthetic oestrogens upon advanced malignant disease. (A. Haddow, J. M. Watkinson, E. Paterson & P. C. Koller) 393-398
 Reactive hypernephritis: case report, with a discussion of the differentiation from islet tumour. (F. T. G. Prunty) 398-400
 Traumatic rupture of the aorta. (G. Forbes) 400-401
 A fatal case of purpura after sulphapyridine. (S. Sherlock & J. C. White) 401-403
 Haemoglobin levels in the Women's Auxiliary Air Force. (S. Yudkin) 403-404

2: 30/9/44

Infantile diarrhoea and vomiting. (M. B. Alexander & Y. Eiser) 425-428
 Inhibition of lactation by hexaestrol dipropionate. (F. Prescott & M. Basden) 428-430
 Factors influencing dermatitis in coal-miners. (R. B. Knowles) 430-432
 Intravenous anaesthesia: continuous positive-pressure drip saline with intermittent pentothal. (W. M. Maidlow) 432-433
 Sympathetic block: proposed therapy in traumatic shock. (D. Engel) 434-435
 The midday school meal: a study of its relation to the total weekly dietary of a group of schoolboys. (R. P. Cook, W. A. Davidson, D. M. Keay & D. G. McIntosh) 443

2: 7/10/44

Surgery in Tunisia: November, 1942, to May, 1943. (J. M. Weddell) 459-462
 Investigation and treatment of enuresis in the army: preliminary report on 277 cases. (P. L. Backus & G. S. Mansell) 462-465
 Post-operative chest complications in gastric surgery. (T. W. Mimpriss & F. G. Etheridge) 466-468
 Two varieties of leukaemia in one family. (R. W. Meikle) 468-469
 Superficial gangrene in adolescent diabetes. (H. Whittaker) 469-470

2: 14/10/44

The control of bacillary dysentery. (R. W. Fairbrother) 489-492
 Plasma acid phosphatase in carcinoma of the prostate and the effect of treatment with stilbestrol. (J. M. Watkinson, G. E. Delory, E. J. King & A. Haddow) 492-495
 Medical experiences in North Africa, 1943-4. (T. C. Hunt) 495-498
 Analgesia in labour: a record of 102 cases treated with pethidine. (J. A. R. Cripps, B. Hall & W. F. T. Haultain) 498-500
 Spontaneous lobectomy. (J. W. Taylor) 500-501

Bulletin of War Medicine

4: August 1944

Gas gangrene. Increased risks and better methods. (War Office. Army Med. Dept. Bull. Supp. No. 15) 687-690
 The soldier's foot. (H. Platt) 690-691

Journal of Neurology, Neurosurgery and Psychiatry

7: January and April 1944

Traumatic dilatation of the cerebral ventricles. (D. W. C. Northfield) 1-6
 The effect of galvanic exercise on denervated and re-innervated muscles in the rabbit. (E. Gutmann & L. Guttman) 7-17
 Myelitis due to vaccination. (G. J. Dixon) 18-20
 The physical examination of two thousand cases of neurosis. (H. G. McGregor) 21-26
 Causation of mongolism. (M. Engler) 27-29
 A case of partial congenital hemi-hypertrophy. (A. Huse) 30-32
 Post-traumatic pain and the causal syndrome. (J. Doupe, C. H. Cullen & G. Q. Chance) 33-48
 A heuristic theory of neurosis. (E. Slater & P. Slater) 49-55

Journal of Obstetrics and Gynaecology of the British Empire

51: August 1944

The clinically suspect pelvis and its radiographical investigation in 1,000 cases. (M. Kenny) 277-292
 Contracted pelvis in childbirth: a study of its morbid effects on mother and child. (H. R. MacLennan) 293-317
 A case of acute inversion of the uterus. (A. E. Chisholm) 318-320
 A case of primary ovarian pregnancy. (O'D. Browne) 321-323
 Caesarian section under spinal analgesia. (R. C. Thomas) 324-329
 Iniencephalus. (S. J. Paterson) 330-333
 A statistical study of the purpose and errors of the routine daily measurement of the puerperal uterus. (C. S. Russell) 334-339
 A case of complete placenta praevia accreta occurring in a primigravida. (D. M. Shotton & C. W. Taylor) 340-343
 Childbirth in the Greek island of Chios in the 6th century B.C., 1780, and 1914. (P. Argenti) 344-349
 Vesicovaginal fistula, foreign body and calculi in bladder following attempted criminal abortion, and normal labour. (R. C. Thomas) 350-352

Journal of Pathology and Bacteriology

56: July 1944

A study of three infants dying from congenital defects following maternal rubella in the early stages of pregnancy. (C. Swan) 289-295
 Massive acute necrosis of the liver: its significance and experimental production. (L. E. Glynn & H. P. Himsforth) 297-305
 Isolation of *Pasteurella septicæ* from an appendicular abscess. (G. B. Ludlam) 307-313
 A consideration of some of the factors concerned in intracutaneous injection of cattle. (W. M. Henderson) 315-325
 Papillitis renis necroticans. (J. Davson & F. A. Langley) 327-333
 The slide test for the serological diagnosis of syphilis. (J. L. Hamilton-Paterson, W. T. S. Cole & G. L. C. Usher) 335-342
 Adenosine compounds and phosphates in the blood of shocked rabbits. (H. B. Stoner & H. N. Green) 343-354
 Pulmonary changes in rabbits produced by bilateral vagotomy. (R. H. D. Short) 355-365
 Some observations on the pathological anatomy of benign prostatic enlargement. (G. I. M. Swyer) 365-375
 The influence of access of free oxygen on the action of antiseptics with special reference to the sulphonamides. (J. W. McLeod, A. Mayr-Harting & N. Walker) 377-389
 A sensitising factor in experimental blastogenesis. (J. C. Mortram) 391-402
 A retroperitoneal digit-containing teratoma. (C. W. Gale & R. A. Willis) 403-409
 Infection of cat-bite and dog-bite wounds with *Pasteurella septicæ*. (E. N. Allott, R. Cruickshank, R. Cyrras-Williams, V. Glass, I. H. Meyer, E. A. Straker & G. Tee) 411-415
 Two cases of lower accessory lung in the human subject. (D. V. Davies & F. W. Gunz) 417-427
 On the use of a modification of Pryce's slide culture method for the estimation of the bacteriostatic power of chemicals on the tubercle bacillus. (H. Muller) 429-433
 The antibacterial action of 4:6-dimethoxytoluquinone. (M. Barber) 434-438
 A method of obtaining permanent preparations for the cytological study of pure cultures of macrophages, with special reference to their mode of division. (F. Jacoby) 438-440
 The staining of eosinophil polymorphs and enterochromaffin cells in histological sections. (A. C. Lendrum) 441
 Two effects of retrograde venous thrombosis in intestinal strangulation. (J. T. Chesterman) 442-443
 A technique for the cutting of frozen sections with the Cambridge rocking microtome. (N. E. Burfitt) 443-445
 Spontaneous folliculosis of the conjunctiva in baboons (*Papio hamadryas*). (J. O. W. Bland) 446
 Experiments with Nile blue sulphate A: its use in demonstrating tract degeneration in the cord. (A. D. T. Govan) 447-449

Lancet

2: 9/9/44

Delayed suture of soft-tissue wounds. (T. R. Sarjeant & W. A. Morton) 333-336
 Systemic administration of penicillin. (I. W. J. McAdam, J. P. Duguid & S. W. Challinor) 336-338
 Dangers of intensive alkali treatment in blackwater fever. (B. G. Macgrath & R. E. Harvard) 338-339
 Hepatitis after yellow fever inoculation: relation to infective hepatitis. I. Clinical and pathological findings. (G. M. Findlay, N. H. Martin & J. B. Mitchell) 340-344
 Unhurried blind intubation. (H. M. Bird) 344
 Return of virility after prefrontal leucotomy: with enlargement of gonads. (R. E. Hemphill) 345-346

2: 16/9/44

Plasma fixation of skin grafts. (J. E. Sheehan) 363-365
 Hepatitis after yellow fever inoculation: relation to infective hepatitis. II. Immunology and epidemiology. (G. M. Findlay, N. H. Martin & J. B. Mitchell) 365-370

Laboratory and clinical trials of patulin. (J. M. Stansfeld, A. E. Francis & C. H. Stuart-Harris) 370-372
 Clinical trial of patulin in the common cold. (Report of the Patulin Clinical Trials Committee, Medical Research Council) 373-375
 Simple method of amputating the thigh. (C. W. G. Bryan) 375
 Congenital malaria in England. (R. P. Gammie) 375-376
 Nutrition and size of family. (J. Yudkin) 384-387

2 : 23/9/44

Late closure of wounds. (P. Clarkson) 395-400
 Inactivation of penicillin by serum. (J. W. Bigger) 400-402
 Oliguria in blackwater fever. (B. G. Macgraith & G. M. Findlay) 403-404
 Unusual response to dicoumarol therapy. (T. Crawford & J. R. Nassim) 404-405
 Mesenteric thromboses in lymphatic leukaemia treated with dicoumarol. (R. A. M. Scott & N. Lissimore) 405-406
 Significance of blood histaminase in pregnancy. (A. Ahlmark) 406-407
 Acute diffuse peritonitis treated with sulphathiazole suspension. (J. T. Chesterman) 407
 Calculation of lung expansion by external measurements of trunk: application to the study of dyspnoea in recruits. (H. K. Goadby) 415-417

2 : 30/9/44

A surgeon looks at two wars. (E. C. Cutler) 427-430
 The constitutional factor in anaesthetic convulsions. (D. Williams & W. H. Sweet) 430-433
 Hyaluronidases in infected wounds. (J. D. MacLennan) 433-434
 Detection of bacterial enzymes in infected tissues. (D. McClean & H. J. Rogers) 434-436
 Neurological complications of relapsing fever. (R. B. Scott) 436-438
 Myxoedema and psychosis. (H. Zondek & G. Wolfsohn) 438-439
 Hypertension associated with unilateral renal lesion. (E. J. R. Leiper) 439-440
 Case of cardiovascular beri-beri. (J. W. Paulley & G. J. Aitken) 440-442
 Stress dyspepsia in industry. (G. P. B. Whitwell) 449-450

2 : 7/10/44

Hazards of hypertherm treatment. (J. Wallace & S. R. M. Bushby) 459-464
 Neurological complications of serum and vaccine therapy. (R. R. Hughes) 464-467
 Clotted haemothorax. (R. W. Lush, J. C. Nicholson, C. R. Stevenson & W. F. Nicholson) 467-470
 Sonne dysentery treated with sulphaguanidine. (W. H. Osborn & R. N. Jones) 470-471
 Sonne dysentery carriers treated with succinyl sulphathiazole. (A. E. Brewer) 471-472
 Bone-marrow infusions for infants. (G. Behr) 472-473

2 : 14/10/44

Desert climate: physiological and clinical observations. (W. S. S. Ladell, J. C. Waterlow & M. F. Hudson) 491-497
 Treatment of staphylococcal infections with penicillin by intermittent sterilisation. (J. W. Bigger) 497-500
 Ovarian fibroma with ascites and hydrothorax (Meigs's syndrome). (R. H. Gardiner & V. Lloyd-Hart) 500-502
 Hereditary familial telangiectasis with epistaxis and migraine. (A. M. G. Campbell) 502-503

Congenital syphilis with obscure initial signs. (C. P. Lapage) 503
 Threadworm infections: prevalence, pathogenicity, periodicity and prevention (C. Lane) 511-513

Public Health

52 : August 1944

Medical supervision in industry in peace and war. (S. A. Henry) 121-126
 The care of the premature infant. (C. F. Brockington) 127

Quarterly Journal of Pharmacy and Pharmacology

17 : April-June 1944

The effect of exercise upon the response of rabbits to insulin. (R. H. Thorp) 75-88
 The comparative activities of atropine, *l*-hyoscyamine, hyoscine and homatropine on mammalian smooth muscle. (D. P. D. Graham & J. A. Gunn) 88-95
 A comparison of some of the ergot alkaloids. Part III. General pharmacology. (A. C. White) 95-102
 The content of active principle in strains of digitalis. (M. Mather & F. J. Dyer) 102-108
 An extended cross-over design and its use in insulin assay. (K. W. Smith, H. P. Marks, E. C. Fjeller & W. A. Broom) 108-117
 A fundamental formula in the statistics of biological assay, and some applications. (E. C. Fjeller) 117-123

Transactions of the Royal Society of Tropical Medicine and Hygiene

38 : August 1944

Blackwater fever anuria. (B. Macgraith) 1-23
 Acute hepatitis without jaundice in West Africa. (R. W. Brookfield) 25-33
 Infective hepatitis in Palestine. (S. Btesh) 35-47
 Rhodesian sleeping sickness in Eastern Uganda. (I. W. MacKichan) 49-60
 Studies in leishmaniasis in the Anglo-Egyptian Sudan. VI. The evolution of Leishmania infections in man. (R. Kirk) 61-70

Tubercle

25 : March-April 1944

Atmospheric environment in relation to the sanatorium treatment of pulmonary tuberculosis. (G. B. Charnock) 19-26
 Situs inversus viscerum, absent frontal sinuses with ethmoid and maxillary infection, and bronchiectasis. Kartagener's triad: report of a case. (W. F. Richards) 27-29
 The pathogenesis of chronic pulmonary tuberculosis. (W. T. Munro) 30-32

25 : May-June 1944

Tuberculous tracheobronchial adenitis in the adult. (G. S. Erwin) 35-43
 Pleural effusions arising from tuberculous tracheobronchial adenitis (primary effusions). (G. S. Erwin) 44-50

BRITISH MEDICAL BULLETIN

Vol. 2 (1944)

No. 12

BACTERIOLOGY

SPECIAL CONTRIBUTIONS

THE DEVELOPMENT OF BACTERIOLOGY IN BRITAIN	
by Sir John C. G. Ledingham	261
VIRUS DISEASES OF MAN : A REVIEW OF RECENT PROGRESS	
by Dr. C. H. Andrewes	265
MODERN LABORATORY METHODS IN THE CONTROL OF TYPHOID AND PARA-TYPHOID-B FEVER	
by Dr. A. Felix	269
HOSPITAL INFECTION : A HISTORICAL REVIEW	
by Dr. R. Cruickshank	272
OBSERVATIONS ON THE CONTROL OF HOSPITAL INFECTION	
by Professor A. A. Miles	276
THE CHEMICAL NATURE OF BACTERIAL ANTIGENS	
by Dr. W. T. J. Morgan... ..	281
THE NATIONAL COLLECTION OF TYPE CULTURES	
by Dr. R. St. John-Brooks	284

REVIEW OF SELECTED PAPERS

Influenza	
Destruction of Influenza Virus by Aerial Disinfection	286
An Outbreak of Influenza B	286
Influenza in Britain, 1942-43	286
A Minor Epidemic of Influenza A	287
Influenza A in October-December 1943	287
Influenza Virus as a Laboratory Contaminant	288
Poliomyelitis : Vaccinia	
Poliomyelitis : Experimental Work in Egypt	288
Poliomyelitis in Troops in the Middle East	289
Ultramicroscopical Studies of Vaccinia Virus <i>In Vitro</i>	289
Typhus	
Inclusion Bodies in Association with Typhus	290
Rickettsial Agglutination Studies	290
Endemic Typhus in Madagascar	290
Vaccination against Typhus	290
Typhus in the Middle East	291
Dry Blood Test for Typhus	291
Technique and Interpretation of the Weil-Felix Test	291
Preparation of Suspensions for the Weil-Felix Test	292
Typhus in Britain	292
Sources and Control of Hospital Infection	
Dust as a Vehicle of Infection in Children's Wards	292
Haemolytic Streptococci in Hospital Dust	292
Hospital Dust : Effect of Daylight	293
Control of Dust-borne Streptococcal Infection	293
Oiled Bed-Clothes : A New Technique	293
Oiled Floors to Control Respiratory Infections	294
Possible Transmission of Haemolytic Streptococci by Flies	294
Scheme for Prevention of Hospital Infection in Children's Wards	294
Design of Dressing Stations	294
Control of <i>Staphylococcus Aureus</i> Infections in a Maternity Department... ..	295
Aerial Disinfection	
Report on Use of Antiseptic Sprays	296
Germicidal Mists and Vapours	296
Propylene Glycol Vapour as an Air Disinfectant : I and II	297
Studies on Wound Infection	
Anaerobic Infections of War Wounds in the Middle East	298
Bacteriology of War Wounds	298
Clinical and Bacteriological Investigation of 708 Wounds	299
Diagnosis of Wound Infection from Bacterial Enzymes	299
Hyaluronidase Production by Haemolytic Streptococci	300
Hyaluronidases in Infected Wounds	300
Detection of Bacterial Enzymes in Infected Tissues	300
Infection of Cat- and Dog-Bites with <i>Pasteurella Septica</i>	300

[continued overleaf

REVIEW OF SELECTED PAPERS—continued

Methods and Apparatus

[illegible]

Various Bacteriological Studies

Nature and Mode of Action of Staphylococcus Coagulase	302
Relative Sterility of Hands of Metal-Workers	303
Bacteriology of Brain Abscess	304
Biochemical Classification of Coliform Bacilli in Sputum	304

BOOKS, MEMORANDA, REPORTS 305

GUIDE TO THE JOURNALS 309

This number of the Bulletin is devoted to reviews of recent work relevant to the study of virus, rickettsial, and bacterial disease. It is not intended to be a comprehensive statement of recent bacteriological work, but is concerned with subjects which are thought to be of special interest at the present time. Work on chemotherapeutic and antiseptic drugs is not included, but will be the subject of a later number.

The first article is the fifth in a series of occasional articles on the development of medical studies in Britain. The author, SIR JOHN LEDINGHAM, contributed this article a few months before his death on October 4th, 1944. Dr. G. F. Petrie, of the Lister Institute, read and corrected the proofs of the article and has contributed the following short note on the author :

"The recent death of Sir John Ledingham has removed a distinguished figure from the ranks of British bacteriologists. His life-long association with the Lister Institute, London, of which he was the director from 1930 until his retirement in 1943, gave him abundant opportunities of keeping in touch with research work in Britain and in other countries. He maintained friendly contact with many of the leaders of medical research throughout the world. His outlook and temper were, indeed, international, and he did much to foster amicable and helpful relations with men of science everywhere, as is witnessed by the notable part he played in the three international congresses of microbiology of the past decade; he was president of the second congress when it was held in London in 1936, and an honorary president of the third congress which met in New York in 1939 at the outbreak of the war. His own contributions to science gave evidence of an unusual width of knowledge, and include studies in pure bacteriology, haematology, immunology, pathology and virus agents. The article which follows bears testimony to the keen interest that he always took in the achievements of the past."

Ledingham had been emeritus professor of bacteriology in London University and bacteriologist to the Lister Institute for 38 years. He was associate editor of the Medical Research Council's "System of Bacteriology" and was appointed a member of the Council in 1934. He was author with Sir Joseph Arkwright of a book on "The carrier problem in infectious diseases" (1912). Further particulars of Ledingham's scientific career are to be found in obituary notices published in the *British Medical Journal* (1944, 2, 514) and *Lancet* (1944, 2, 550).

DR. C. H. ANDREWES is well known as one of the foremost authorities on virus disease. He obtained his medical education at St. Bartholomew's Hospital, London, where he subsequently had several resident clinical appointments. From 1923-25 he was assistant resident physician at the Hospital of the Rockefeller Institute, New York City, and since 1926 he has worked at the National Institute for Medical Research, Hampstead (London), where he has been engaged almost entirely in the study of viruses, especially their immunology, their relation to tumours, and the influenza viruses. In 1933 Andrewes discovered, with Professor Wilson Smith and the late Sir Patrick Laidlaw, that influenza was due to a virus which would infect ferrets and mice. This important discovery

was the beginning of the scientific study of the difficult problem of influenza.

The name of DR. A. FELIX will be familiar to all readers from his association with the Weil-Felix reaction for the diagnosis of typhus fever (1916). In more recent years Felix has established the value of this and similar reactions in the differentiation of rickettsioses throughout the world. He has also been responsible for work on the antigenic analysis of bacteria, in particular the recognition of the H, O, and Vi antigens. This work has opened a chapter in serology and provided new methods of distinguishing closely-allied bacterial species and of dealing with problems of passive and active immunity. Since 1927 Felix has been a member of the scientific staff of the Lister Institute from which he has, during the war, been seconded to the Emergency Public Health Laboratory Service (Medical Research Council).

DR. R. CRUICKSHANK has been pathologist in charge of a *Group Laboratory in the London County Council Hospital and Medical Services* since 1936. He was lecturer in bacteriology in the *University of Glasgow* and bacteriologist to the *Glasgow Royal Infirmary* from 1928 to 1936. He received his early training in the bacteriology departments of *Glasgow and Aberdeen Universities* and did 3 years' clinical work in *paediatrics and fevers*. He has contributed to the literature on *intestinal flora and intestinal infections, puerperal sepsis and the bacteriology of the genital tract, scarlet fever, pneumonia, pertussis and air-borne infection*. He gave the *Milroy Lectures of the Royal College of Physicians* on "*Pneumococcal infections*" in 1933 and was a *Chadwick Lecturer* in 1943. He is joint-editor of "*Control of the common fevers*" (1942) and is a member of the *Medical Research Council committees on hospital cross-infection, protein requirements, and measles prophylaxis*.

He has played an important part in the revival of interest in the mechanism and control of infections acquired in hospital, and is thus exceptionally well qualified as author of a historical review of this subject.

PROFESSOR A. A. MILES, who contributes a review of modern views on the same subject, was educated at Cambridge and St. Bartholomew's Hospital. He was demonstrator in bacteriology with the late Professor W. W. C. Topley at the London School of Hygiene (1929-31), and then demonstrator in pathology at Cambridge until 1935. He then became Reader in bacteriology at the British Postgraduate Medical School, London, until he was appointed professor of bacteriology at University College Hospital Medical School (London University). For the past 5 years he has also been pathologist-in-charge of the London Sector IV of the Emergency Medical Service (Ministry of Health). His scientific activities have been mainly concerned with the immunological problems arising from antigenic analysis of bacteria. As a result of the war he has been involved in the study of cross-infection of wounds, but his interests are more in the general problems of epidemiology of wound-infection, both in war wounds and in industrial wounds, and in the special problems of infection

with anaerobic bacteria. In connection with industrial wounds, he has recently worked at the Medical Research Council's Wound Infection Unit attached to the Birmingham Accident Hospital.

DR. W. J. T. MORGAN is a member of the staff of the Lister Institute and Reader in biochemistry in the University of London. A note on his work appeared in Vol. 2, No. 8-9, of this Bulletin, to which he contributed a review on the "Occurrence and nature of human blood-group substances".

DR. R. ST. JOHN-BROOKS is curator of the National Collection of Type Cultures, which he describes and discusses in his article. He is permanent secretary of the Nomenclature Commission, and secretary of the National Committee for Great

Britain and Northern Ireland, of the International Association of Microbiologists. He is also secretary of the recently-formed Medical Research Council Committee on Research in Medical Mycology and joint-secretary of the new Society for General Microbiology. Earlier he was special bacteriological investigator to the Local Government Board (1911), special sanitary investigator to the Governments of the Windward and Leeward Islands (1912-14), secretary to the Commission for Plague Investigation in India (1914-15), and specialist in bacteriology to the County of London War Hospital (1915-19) and to the Royal Army Medical College, Millbank (1919-20). He was secretary to the Second International Congress for Microbiology (London, 1936) and president (section 1) of the Third International Congress at New York (1939).

REVIEW OF SELECTED PAPERS. Contributions to this section have been received from Professor A. W. Downie, Professor L. P. Garrod, Dr. J. C. Cruickshank, Dr. M. A. Jennings, Dr. D. McClean and Dr. A. Macdonald

SPECIAL CONTRIBUTIONS

550

THE DEVELOPMENT OF MEDICAL STUDIES IN BRITAIN: V. BACTERIOLOGY

the late SIR JOHN C. G. LEDINGHAM, C.M.G., F.R.S.

The purpose of this article is to sketch the development of the science of bacteriology in Britain from its early days some seventy years ago, when a few scattered workers were striving to gain acceptance for the germ theory of infectious disease, to the world-wide and intensive researches of modern times with numerous workers contributing to knowledge which is constantly being applied to the solution of public health problems. Nowadays, increased and speedy inter-communication between men of science through special societies, scientific journals and international congresses has tended to make the research programmes of individuals and teams in different lands more or less similar, at least in general scope. The layman, too, by means of the radio, popular digests, and the public press, has now many opportunities of becoming acquainted with the powers of bacteria for good or ill and the part these play in a truly astonishing variety of natural processes.

An appreciation of bacteria as living entities fulfilling definite functions in nature came long after the demonstration in the seventeenth century of his "little animals" by Leeuwenhoek of Delft, who detected them by aid of his simple hand-made lenses and described his observations in a long series of letters to the Royal Society of London of which, in the year 1680, he was made a Fellow.

The real commencement of the bacteriological era dates from the fifties and sixties of last century, when Louis Pasteur, after finally disposing of the abiogenesis theory which had been a matter of controversy for a hundred years and more, turned his attention to the study of fermentation processes as observed in the manufacture of wine, beer and vinegar, and demonstrated conclusively that living and multiplying yeast cells were responsible for the observed phenomena. Others before him had come very near the truth, but the novelty of Pasteur's work and the failure of otherwise highly distinguished men of science of the time to comprehend it, was attested by the obstinate opposition of such men as Liebig and some of Pasteur's own compatriots. It will be remembered that Pasteur's final demolition of the abiogenesis belief failed to convince the British scientist, Charlton Bastian (1837-1915), who never ceased to maintain his own point of view.

Incredulity, indeed, was by no means confined to the ignorant and uneducated, as Lister also experienced when his antiseptic principle was first given to the world in 1865-67 at a time when Pasteur had turned to the investigation of silkworm disease. Before Pasteur's work on fermentation, studies of the larger fungi had been made and were greatly helped by improvements in the compound microscope in which British microscopists, notably Joseph Jackson Lister,

father of Lord Lister, had taken a most important part. These studies had led to the recognition in the eighteenth-thirties and -forties of fungal parasites in association with certain skin diseases of man such as ringworm and favus. In 1865 the association of the much smaller bacteria with infectious disease had not really been made an object of experimental enquiry, though this idea was certainly present in the mind of Pasteur as an extension of his experience with diseases of beer due to the work of wild yeasts. It was not, however, until the late seventies and early eighties that he was to make his great contributions to preventive medicine.

Achievement of Lister as a Bacteriologist

In 1865, when Lister, then Professor of Surgery in Glasgow, learned, largely by chance, of the work of Pasteur showing the dependence of the fermentation processes studied by him on the metabolism of the yeast cell, he was, so we are told, at once inspired with the notion that the "putrefactive" processes which he had sadly noted in surgical wounds and upon the causation of which he had long reflected, might also be due to the work of living microscopic agents. The revelation came to him in a flash and his reaction to it, like that of Pasteur when faced with a similar problem, was to attempt to control the morbid process without enquiring too closely into the nature and properties of the specific causative bacteria. Lister and Pasteur were essentially early exponents of preventive medicine, the one seeking to attack directly the presumed parasites that cause the festering of wounds, the other to immunize the host against the risk of an attack by invading germs in a virulent form. It is, indeed, remarkable that each of these principles has proved its worth in its own sphere of action, that of Pasteur having abundantly confirmed and extended the work of Jenner, on which Pasteur's use of artificially attenuated cultures was admittedly based.

Lister's antiseptic principle took root slowly, as is well known, and with its full recognition as an essential element of good surgery, its tardy universal adoption now gives us merely cause for wonder. Did Lister's discovery of the antiseptic principle make him a bacteriologist? In 1865 he knew little or nothing of bacteria and their ways beyond the fact that their access to wounds could be prevented by the use of such chemicals as carbolic acid, but Lister was not content with this knowledge. He resolved to make himself a bacteriologist quickly—and in the early years that followed his discovery of the antiseptic method, while a professor of surgery in Edinburgh, he spent the spare hours he was able to snatch from his professorial duties in an intensive study

of bacteria and fungi. He invented for his own use a complete bacteriological armamentarium together with ingenious accessories which enabled him to study both fungi and bacteria with a high degree of accuracy and under sterile conditions. Sir Charles Martin has, indeed, remarked in the course of a Lister Memorial Lecture "I doubt whether bacteriologists are aware that Lister invented all their methods before 1870". He made his mistakes both of interpretation and of technique but he was always ready to acknowledge them and to improve his methods. Moreover, by 1874, he had established a correspondence with Pasteur which was profitable to both. The fermentation and curdling of milk deeply interested Lister and he made a study of the factors which are involved in the process. With the aid of an ingenious syringe which he invented and which was capable of delivering minute quantities of fluid, he succeeded in securing a pure culture of the organism mainly responsible for the reaction, namely, *Bacterium lactis*. This is believed to be the first pure culture obtained of any organism. The great discovery of the use of solid media as an aid to the isolation of pure cultures of organisms was yet to come. It was made by Robert Koch (1843-1910), whose conclusive proof that *Bacillus anthracis* was the cause of anthrax appeared in 1876, and was soon followed by his experimental demonstration of micrococci as causative agents of wound sepsis. In the year 1881 Koch demonstrated his solid-culture method at the International Congress of Medicine in London in the presence of Pasteur and Lister and we can, even at this date, understand the surprise and pleasure of these two pioneers when they realized the importance of the discovery for the future of bacteriological practice. It has been remarked that in the rapid development of bacteriological knowledge which followed Koch's early discoveries, neither British nor American workers took any large share, and in a certain sense this is true and will be explained later. Nevertheless, in the opinion of the writer, had Britain possessed no exponent of bacteriology but Lister at the commencement of the bacteriological era, this country would have been adequately represented. The truth is that Lister's achievements in bacteriology have long been overshadowed by the pre-eminence of his work for surgery. Between the years 1873 and 1881 he communicated to the press only six substantial papers on his bacteriological pursuits, which were carried on at night and in the early morning when he was free from the preoccupations of his routine work.

In a summary of British achievements in the sphere of bacteriology at this early date, one cannot omit mention of the work of John Tyndall (1820-1893) whose observations and experiments on the floating matter of the air in relation to putrefaction and infection appeared in 1881. Lister abandoned the carbolic spray as an aid to antisepsis in 1887, when he was satisfied that the organisms in dust played little or no part in the causation of wound sepsis, and that in any event the spray was powerless to destroy them. In his address to the Surgical Section on the International Medical Congress held in London in 1881, Lister made the remark, "It must be distinctly borne in mind that the spray is, beyond all question, the least important of our antiseptic means, and that the circumstance that a surgeon does not happen to have a spray-producer at hand is no excuse whatever for abandoning the attempt to obtain aseptic results." He was, in fact, convinced that the organisms most to be feared were those on the skin of the patient and the hands of operators and attendants. At the present time, with the knowledge we possess of the frequent presence of specific pathogenic organisms discharged into the air from septic dressings or expelled from the throats of doctors, nurses or patients, physicians and surgeons are finding it very important to take steps to control this additional source of infection in hospital wards. The carbolic spray which Lister had rightly abandoned as useless has its modern counterpart in the attempts to destroy infective germs and ultramicroscopic agents of disease in the atmosphere of rooms by aid of disinfectants in "aerosol" form.

Lister as a Pioneer in Immunology

Lister, from his earliest approach to the surgeon's calling, had pondered much over the sequence of changes, whether morbid or otherwise, that take place in wounds and more particularly over the probable factors that make possible the healing of wounds under conditions permitting the access of saprophytic germs, for example, from the air. He had

come to the conclusion that blood must possess some peculiar property of destroying such germs. This idea he put to the test by exposing fresh blood to air in sterile vessels when he found that putrefaction did not readily take place. A more elaborate and convincing proof came from an experiment in which he withdrew blood from the jugular vein of an ox into tubes, allowed it to clot, and added to the exuded serum tap-water in varying amounts. It was found that even at the temperature of the body, putrefaction did not take place when as much as eight drops of tap-water were added. The addition of putrid blood in minute quantities also failed to infect, nor did the addition of dust cause any putrefactive change within a reasonable period of time. He had thus independently demonstrated the presence in serum of a bactericidal agent which a few years before had been postulated by Lewis and Cunningham and later had been more elaborately studied by Fodor (1886) and by Nuttall (1888). This property of serum is almost certainly of great importance in natural defence. Further, in the course of experiments performed by Lister at the École Vétérinaire, Toulouse, he had carefully noted the changes which took place in vascularizing clots artificially produced in the jugular vein of an ass, and had observed the appearance of multitudes of "new living elements" whose function was a mystery to him until Metchnikoff's work on phagocytes appeared towards the close of the eighties.

Rapid Advances after Koch's Early Discoveries

The decade 1880-90 witnessed a succession of spectacular discoveries of disease agents, largely owing to Koch's having placed in the hands of students of bacteriology an equipment and a scheme of technical procedure which greatly facilitated the isolation and recognition of the bacterial agent responsible for the disease under study. Many authorities would date the commencement of modern bacteriology from this period. Pupils flocked to Koch's Institute in Berlin from his own country, and from many foreign countries including Britain, to understudy the master and subsequently to disseminate the new knowledge. At this time the output of newly discovered agents of infectious diseases was essentially the work of Koch or his pupils. In Britain there was no such centre of research. This had to await the return of students who had worked under Koch or elsewhere in Germany and the wide diffusion by translations of outstanding bacteriological texts. Lister was too occupied to found a school of bacteriology, though he alone was capable of doing so. Watson Cheyne, the surgeon who accompanied Lister from Edinburgh to London in 1877 and who, like his chief, had an active interest in bacteriological problems that were the concern of the surgeon, studied and worked for a time with Koch and later did excellent service by making known to English readers, through his books, the achievements of the new science. Edgar Crookshank (1858-1928), who studied in various German laboratories and later established the first bacteriological laboratory in London at King's College, produced in 1886 a *Manual of bacteriology*, which still occupies an important place among the early bacteriological handbooks and is particularly valuable for its comprehensive references to papers up to that time in all branches of bacteriology. Lister and Watson Cheyne, with Alexander Ogston (1844-1929) of Aberdeen, made a trio of bacteriologist-surgeons whose original work worthily represents British effort in the field of bacteriology at this early period. Ogston during 1880-83 carried out fundamental research on the micrococci present in abscesses, thus completing and amplifying Koch's contribution to the subject in 1878. By cultural methods, a special staining technique, and inoculation of cultures into experimental animals, he proved in a masterly manner that abscesses in man of the acute type invariably contain micrococci and that these latter are of two kinds and are distinguishable by their manner of arrangement in stained films of the pus. He distinguished the *Streptococcus* of Billroth from another form, resembling bunches of grapes, which he named the *Staphylococcus*. Ogston's work greatly clarified the hitherto rather confusing picture presented by coccal parasites in these abscesses and in septic processes generally.

Lister's boldly conceived principle of antisepsis, which was based on the firm belief that "putrefaction" of wounds must surely, like other processes studied by Pasteur, be the work of micro-organisms, became in Britain, as was natural in the first instance, the province of surgeons eager to acquire a more intimate knowledge of the types of bacteria which are

liable to frustrate their surgical skill and endeavour. Outside the ranks of the surgeons there were at the time (the eighties) in Great Britain few if any trained pathologists with the exception of Greenfield of Edinburgh, who were attracted to the new study. The reason is that a chair of pathology, except in Scotland, did not then exist in Britain. The most prominent representatives of experimental medicine in Britain during the seventies were physiologists, headed by the veteran William Sharpey. Their work was in the main confined to histology and microscopy, but after the formation of the Physiological Society in 1876, followed two years later by the foundation of the *Journal of Physiology*, the experimental aspect of the subject became and has continued to be, in Britain, the research field of a long succession of distinguished exponents whose names are household words throughout the world. Cambridge University and University College, London, have long been, perhaps, the most favoured centres of their labours. The incursion of physiologists into bacteriology, at a time when reports of the early discoveries of specific micro-organisms in infectious disease were being made, was not a particularly happy venture, for the new subject of enquiry demanded a novel and difficult technique, and the correct interpretation of bacteriological findings derived from cultivation methods required considerable experience which few then possessed. It is noteworthy that the physiologists paid great attention to the probable mechanism, in the light of purely physiological principles, of the pathological lesions they found at necropsies (of suspected cholera cases), irrespective of whether the cultures yielded Koch's vibrio or not. The bacteriologist of to-day would welcome collaboration with the physiologist, for there are many aspects of bacterial activity, such as the nature of the interactions of host and parasite at their earliest contacts, which would be likely to receive illumination from his special methods of study. Their partnership could hardly, nowadays, be followed by such a strange happening as Lister's warning against the easy acceptance in 1881 of Ogston's work on the causative role of the staphylococcus in acute abscesses, on the ground that the phenomena of inflammation which he had carefully studied as a young post-graduate under the inspiration of Sharpey, might conceivably include suppuration as an end-result of nervous influence on the blood vessels. Lister attached cardinal importance to this influence and attributed to it such results of counter-irritation therapy as he had observed. Ogston replied effectively to the criticism and, needless to say, Lister quickly revised his opinion.

Modern Period

Towards the close of the 19th century it became obvious to men of vision in Britain that a specially trained cadre of bacteriologists was absolutely essential to ensure the future progress of the science in this country. The marvellous work of Pasteur during his declining years, and in particular his studies on the control of rabies (1884), the novel and fascinating researches of Metchnikoff, and the interest excited by the discovery of diphtheria and tetanus toxins and their corresponding antitoxins, all served to emphasize the necessity of concentrating bacteriological research in special institutes and in departments of pathology of the universities and of the large voluntary hospitals. In 1891 the *British Institute of Preventive Medicine*, later to be renamed the *Jenner Institute* and finally the *Lister Institute*, was incorporated and, commencing its research career in 1893, has now half a century of performance to its credit in many fields of experimental medicine including that of bacteriology and microbiology generally. During this time it has afforded research facilities to many workers both from the British Commonwealth and from foreign lands.

The circumstance that the staff of a research institution usually includes experts in the basic sciences such as biochemistry and biophysics, has the effect of raising the quality of the work, always provided that the fullest liaison exists between the workers in the various fields. The lack of clinical material may, at times, be seriously felt and should, if at all possible, be made good by the provision of research hospital-units attached to the institution. There can be little doubt that in the future the facilities offered by research institutions to workers from abroad will be greatly extended, and that this will operate to the certain benefit of science and to the cause of international amity.

Some thirty years ago, under the terms of the National Health Insurance Act (1911), financial provision was made for medical research, and was followed by the formation of the *Medical Research Committee* (later the *Medical Research Council*) working under the Privy Council and responsible not only for the conduct of medical research in a special institute (*National Institute for Medical Research*) but also for the financial support of research in many branches of medicine undertaken by selected workers throughout the country. The value of the services of the *Council* to medical research, including bacteriological science, has been incalculable, and the investigations of its experts in the *National Institute*, together with the reports of its special enquiries and surveys (*M.R.C. Special Report Series*), have long been known and appreciated throughout the world.

Research and Teaching

Bacteriological research has long been pursued in the pathological departments of all the British universities and many of the large voluntary and municipal hospitals. In addition, there have, for some time, been chairs of bacteriology in the great majority of the universities, where not only medical bacteriology, but also bacteriology as applied to agriculture and industry, is taught and studied. At Cambridge, since 1924 when pathology was included as a subject in Part II of the *Natural Sciences Tripos*, more than half the time of the course is devoted to bacteriology. The veterinary world possesses a number of institutions such as the *Royal Veterinary College*, the *Institute of Animal Pathology* at Cambridge, and the Veterinary Research Department of the Ministry of Agriculture, in which active work is conducted on bacterial and virus diseases of farm animals.

Recently-introduced equipment such as ultracentrifuges of the Svedberg and other types, electrophoresis apparatus, and electron microscopes, are now available in one or other of the various institutions I have mentioned above, so that the visitor from abroad who wishes to put his ideas to the test will have no difficulty in finding facilities adequate for his purpose.

Bacteriology as applied to hygiene, sanitation, epidemiological enquiry, and the diagnosis of infectious disease, has been practised in Britain from a very early period. During the present war facilities for applying bacteriological methods in the field of hygiene have been greatly augmented by the provision of many additional laboratories throughout the country under the Emergency Public Health Laboratory Service organized by the *Medical Research Council*.

At Cambridge University in 1875 the first Diploma in Public Health was established, and this example was followed by universities and licensing bodies. Bacteriology and serology have always formed an important part of the instruction for this diploma. Courses leading to a post-graduate diploma in bacteriology were established in the University of Manchester by the late Professor W. W. C. Topley in 1923 and served, no doubt, as the pattern from which Topley developed the courses in the *London School of Hygiene* for the academic Diploma in Bacteriology of London University.

Outside the purely medical fields there have, for many years, been departments in the large agricultural and dairy research institutes for the study of bacteriology and protozoology in relation to the soil, to plant diseases of bacterial and virus origin, and to the numerous problems of the dairy industry. I need mention only such institutes as the *Rothamsted Experimental Station*, known the world over for its services to agriculture, the *National Institute for Research in Dairying* at Reading, the *Hannah Dairy Research Institute* in Ayrshire, and the *Rowett Institute* in Aberdeenshire. Many industrial firms, or combinations of such, also have their research departments in which studies of bacteria, or it may be of fungi and protozoa, are conducted in so far as they concern the particular industry whether it be brewing, leather manufacture, or the search by chemical and pharmaceutical firms for new substances of chemotherapeutic importance. A long list of such firms could be cited.

Technical schools (polytechnics) in the larger cities arrange also for the teaching and study of this subject which, indeed, would seem to enter more and more into the register of commitments essential for industrial progress in many fields.

A subdivision of microbiology, and a very important one to which I have not yet alluded, is protozoology, particularly in its relation to animal diseases. It will suffice, however,

to state that the study of protozoa as causative agents of disease has long been intensively pursued in the great Schools of Tropical Medicine in London and Liverpool, the *Wellcome Bureau of Scientific Research*, and in the universities, for in this sphere of enquiry Britain can boast a line of pioneers, many of them of Scottish birth (e.g. Manson, Ross, Bruce and Leishman), whose names have been known throughout the scientific world for at least half a century. In recent years the term Microbiology has come to connote a study which treats of virus agents, protozoa and microfungi in addition to bacteria, and it is significant that three international congresses for microbiology, held respectively in Paris, London and New York during the past decade, adopted this convenient term and reported progress in all those subjects which are concerned with the activities of living microscopic and submicroscopic agents.

Literature

The purely specialist journals published in Britain which contain or may contain papers on microbiology (including bacteriology, virus research, protozoology, and mycology) are the following: the *Journal of Pathology and Bacteriology*, the *British Journal of Experimental Pathology*, the *Journal of Hygiene*, the *Journal of Dairy Research*, the *Annals of Applied Biology*, the *Transactions of the British Mycological Society*, the *Abstracts of the Society of Agricultural Bacteriologists*, and *Parasitology*, but many important papers have first seen the light in the *Proceedings of the Royal Society (Series B)*, the *Lancet*, and the *British Medical Journal*; in recent years, *Nature*, like *Science* in the United States of America, has given early publicity in its columns to new or promising developments. The *Transactions of the Pathological Society of London*, whose long history came to an end when the Royal Society of Medicine was founded, the *Philosophical Transactions of the Royal Society of London*, and the *Quarterly Journal of Microscopical Science* contain many of the earlier contributions to bacteriology published in Britain during the last quarter of the past century.

The *Tropical Diseases Bulletin* and the *Bulletin of Hygiene*, now in their 41st and 19th volumes respectively, contain *inter alia* valuable abstracts and reviews of current microbiological research. Both are issued under the direction of the Honorary Managing Committee (appointed by the Secretary of State for the Colonies) of the *Bureau of Hygiene and Tropical Diseases*, Keppel Street, London, W.C. 1. [This Bureau also publishes, on behalf of the *Medical Research Council*, a *Bulletin of War Medicine*, now in its fifth volume.]

I cannot fail to allude here to at least five outstanding additions to general knowledge and to the history of bacteriological science, viz.: (i) *The history of bacteriology* by the late Professor William Bulloch, to which I have often had to refer while compiling this sketch; (ii) *A system of bacteriology in relation to medicine* in nine volumes, written by British workers and published between the years 1929–31 by His Majesty's Stationery Office under the aegis of the *Medical Research Council*; (iii) the very notable and comprehensive treatise, *Principles of bacteriology and immunity*, by the late Professor Topley and his colleague Professor G. S. Wilson of the *London School of Hygiene*; (iv) *Diphtheria: its bacteriology, pathology and immunology*, written by seven members of the Bacteriological Committee of the *Medical Research Council* and published in 1923 by His Majesty's Stationery Office; and (v) *Antony van Leeuwenhoek and his "little animals"*, by Clifford Dobell (London, 1932): a masterly treatise on the life and work of the discoverer of bacteria.

Some Twentieth-Century Contributions

It would be a difficult task to attempt in a short article any detailed survey of British bacteriological studies during the past half-century, but I may usefully draw attention to some notable advances dating from the commencement of the present century:

i. The contributions to immunology in the early years of the century, with particular reference to the prophylaxis of enteric disease. Such studies have since been actively pursued as the need for control of the manufacture and standardization of biological products, particularly therapeutic sera, became more and more acute, and as the urge arose to explore the mechanism of antibody-production, the chemical nature of antigen and antibody, and their manner of union (immunochemistry).

ii. The work of the Tuberculosis Commission, which revealed the importance of bovine tubercle bacilli as causative agents of tuberculosis in man.

iii. The experimental demonstration of the transmission of bubonic plague by the rat-flea.

iv. The work of the Mediterranean Fever Commission, which incriminated the goat as the reservoir of the causative agent, discovered in 1887 by David Bruce, and also the work of the *Royal Society's* Sleeping Sickness Commission.

v. The pioneer researches into anaerobes and their differentiation carried out by a team of workers during and after the war of 1914–18.

vi. The new knowledge relating to bacterial variation during the first decade, and the later contributions on the antigenic constitution of the enteric and food-poisoning groups of bacteria.

vii. The work on experimental epidemiology by the late Professor W. W. C. Topley and Professor M. Greenwood at the *London School of Hygiene*.

viii. The elaboration of a trustworthy and efficient prophylactic agent against diphtheria (A.P.T.) now widely used throughout the world and emanating from the *Wellcome Serum Laboratories*.

ix. The differentiation and significance of the *gravis*, *mitis* and *intermedius* types of *C. diphtheriae* by workers of the *Leeds school*.

x. The contributions of the late Dr. F. Griffith and the late Dr. W. M. Scott, both victims of enemy action during the present war, to the serological typing of streptococci, and its application to such problems as the mechanism of origin of puerperal sepsis and ward infection.

xi. The contributions of biochemists to the study of bacterial metabolism and nutrition, commencing with the pioneer studies of the late Arthur Harden of the *Lister Institute* and continued there and also at the Biochemical Department of the University of Cambridge, the Department of Bacterial Chemistry of the *Medical Research Council*, the Bacteriological School of *Leeds University* and other centres.

xii. The discovery of bacteriophage at the *Brown Institution* by F. W. Twort.

xiii. Chemotherapeutic investigations in protozoal and bacterial disease, including the discovery of penicillin by Fleming at *St. Mary's Hospital* and the development of this discovery by Florey and his colleagues at Oxford; and the contributions to the chemotherapy of certain protozoal diseases by the late Professor Warrington Yorke and others.

xiv. The substantial contributions of British workers during the past two decades to our knowledge of virus diseases and of virus agents, particularly the discovery of a virus associated with influenza made at the *National Institute for Medical Research*; and the enquiries into the nature of virus bodies, such as those of vaccinia and smallpox, described originally by Buist in the eighties of the last century, independently rediscovered by the late Professor Paschen, but only in recent years in Britain rendered capable of isolation in a pure state and proved to be the actual causative agents of the diseases in question. These bodies, whether of plant or of animal origin, have now become the subject of intensive chemical and biophysical study both in this country and in the U.S.A.

This brief recital of notable advances must for the moment suffice. Further rapid progress may be expected in the future as the solution of the numerous problems presented by microbiology engages more and more the interest and assistance of experts in the basic sciences. A firmer liaison than now exists in Britain between workers in the various fields of microbiology would seem to be highly desirable for the discussion of common problems, and it is hoped that this desideratum may be realized in some effective way in the post-war period.

In conclusion, I cannot omit mention of the services rendered to bacteriologists in all spheres of work and in many lands by the *National Collection of Type Cultures*, located at the *Lister Institute*, with the financial support of the *Medical Research Council*.

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Lord Lister, by Sir Rickman John Godlee (Oxford, 3rd ed., 1924).

The *Medical Research Council Special Report Series* [248 of these reports have now been published by H.M. Stationery Office; they include a very large number dealing with bacteriology and public health problems and first appeared in 1915. The *Catalogue of the National Collection of Type Cultures* is No. 214 of the series]. Sir Charles Martin's Harveian Oration, *Lister's early bacterio-*

logical researches and the origin of his antiseptic system, appeared in *Med. J. Aust.*, 1932, 2, 437.

Obituary notices of the earlier British workers in bacteriology are to be found in the *Proceedings of the Royal Society Series B*, the *Journal of Pathology and Bacteriology* and elsewhere; for references, see Bulloch's *History of bacteriology*.

551

VIRUS DISEASES OF MAN: A REVIEW OF RECENT PROGRESS

C. H. ANDREWES, M.D., F.R.C.P., F.R.S.

National Institute for Medical Research

The subject of virus diseases is now so extensive that a review such as this cannot attempt to cover it all. The writer must, therefore, confine himself primarily to the diseases affecting man and consider only those aspects in which he judges that the greatest progress has recently been made. No attempt will be made to go deeply into the large and controversial subject of the nature of viruses, and many other subjects such as the relationship of viruses to tumours will also have to be omitted.

New Biological Techniques

Viruses are known by their small size, their inability to grow on lifeless culture media, and their dependence for multiplication on a habitat within living cells, whether animal or vegetable. New methods for studying them, many of them expensive and complicated, have been evolved in recent years; but ultimately almost all work on viruses is limited by the need for a susceptible laboratory animal. Diseases of veterinary importance affecting cattle, sheep, horses or poultry can, if necessary, be studied by experiments on the affected species, though this is often a costly business; but for the study of human virus diseases a convenient small laboratory animal is of prime importance. Fortunately, the rabbit, the guinea-pig or the mouse can be infected with many important viruses, such as those of vaccinia, herpes simplex or yellow fever; but some human viruses will infect only rhesus or other species of monkey; examples are mumps, measles and trachoma. The only animal reported as being susceptible to the virus of the common cold is the chimpanzee.

Progress has been made in recent years by successful search for "new" laboratory animals, more convenient and less expensive than chimpanzees and monkeys. The use of the ferret by Laidlaw & Dunkin (1926) in their work on dog distemper introduced that animal to the virus-laboratory, and it has been widely used since the discovery (Smith, Andrewes & Laidlaw, 1933) that it can be infected with influenza. In 1939 Armstrong transmitted a strain of poliomyelitis virus to the cotton-rat, *Sigmodon hispidus*, a rodent commonly found in the United States and not unlike an ordinary brown rat but with longer fur. Since then cotton-rats have been profitably used for the study of many virus diseases. They readily breed in captivity—needless to say a most important asset for any candidate for the post of a laboratory animal. Other rodents such as golden hamsters (*Cricetus auratus*) and voles (*Microtus arvensis*) also breed readily and are likely to be useful; and trials with yet others are reported with increasing frequency.

Kunkel (1943) has lately emphasized the advances which have accrued from the introduction of new species of plant hosts into the studies of plant viruses, and it seems likely that the same will apply in the case of animal viruses, though greater difficulties are involved. There are human diseases almost certainly due to viruses but not yet transmitted to species other than man—such are herpes zoster, molluscum contagiosum, dengue, sandfly fever and infectious hepatitis. Workers have shown much zeal in attempting transmission to whatever in the way of a menagerie they could obtain. But many animal-viruses will only infect one host-species. It is likely that, in the case of some human virus diseases, we shall have to be content for the present with the information obtainable from experiments on human volunteers, and even that much knowledge we may have to forgo if the disease is too dangerous for experiments on man.

The new "laboratory animal" which has yielded by far the best dividends is the fertile hen's egg. Embryonic tissues,

whether in the living egg or in tissue-culture, will support the growth of many viruses which will not survive in newly hatched chicks. Woodruff & Goodpasture (1931) introduced the technique of growing viruses on the chorio-allantoic membrane of hens' eggs, and Burnet (1933) further developed it, particularly by describing a method for making an artificial air-sac over the area of membrane which it was desired to infect. This new technique is now in use in almost every virus-laboratory. Some viruses will produce isolated countable lesions on the membrane, so that a virus-suspension can be titrated, much as are bacteria when inoculated on agar in a Petri dish; further, the technique can be applied to the titration of immune-sera and to other studies. Another advance came from Goodpasture's laboratories (Buddingh & Polk, 1939), and again this was developed by Burnet (1940): viruses were inoculated into the amniotic cavity of the developing embryo and thus almost directly into its respiratory tract. Cox (1938) first introduced viruses into the embryo's yolk-sac, and this technique is the basis of modern methods of cultivating the rickettsiae of typhus fever for vaccine manufacture. So, for various purposes, viruses may nowadays be injected either on to the chorio-allantoic membrane, or into the amniotic, allantoic or yolk-sac cavities or directly into the body of the small embryo.

Nor does this exhaust the use of the chick-embryo. Goodpasture & Anderson (1944) have sought to overcome difficulties due to a lack of species susceptible to human viruses, by grafting human skin or other tissues on to chick chorio-allantoic membranes and infecting them while they are surviving there. In this way, they have infected human tissues *in ovo* with the virus of herpes zoster, showing that they have done so by demonstrating characteristic "inclusion bodies" in the nuclei of infected cells.

Finally, minced chick-embryo is the favourite medium for growing viruses in tissue-cultures. Probably most viruses which are accessible to laboratory study at all, have been grown in tissue-cultures. For many, the simplest techniques suffice; it is only necessary to mince up some of the chosen tissue, suspend it in a modified saline (Tyrone's solution) in a suitable small glass vessel, add some virus and incubate at 37° C. In these instances the animal tissues are infected while merely surviving, not multiplying. But for other viruses, one has to add serum or plasma to the medium, to observe greater care as to its composition and to use the more elaborate techniques which ensure that the cells not only survive, but remain reasonably healthy and multiply. Propagation of viruses in tissue-cultures is proved by grinding them up and testing them for the presence of virus by animal-inoculation (while making due allowance for the possibility of mere survival), by finding characteristic pathological changes in cells such as "inclusion bodies" or by detection of alterations in the growth of the cultures.

Erythrocyte Agglutination by Viruses

Recently Hirst (1941, 1942)—and, independently, McClelland & Hare (1941)—noted when opening chick-embryos infected with influenza virus that erythrocytes from accidentally cut vessels of the chick-embryo were agglutinated when the blood flowed into the allantoic fluid. No such agglutination occurred in the case of uninfected embryos. Further work showed that it was, in fact, the adsorption of influenza virus itself on to the erythrocytes that caused the agglutination. Here was the basis of a very elegant and convenient technique for quantitative studies of influenza, and workers have not been slow to make use of it. Cells of adult fowls, and, rather less

conveniently, of other species such as guinea-pigs or human beings (group O) can be used. Virus can be estimated quantitatively and so can antisera, for in the presence of the appropriate antiserum specific agglutination of erythrocytes does not occur. Influenza virus, treated with formalin or stored for long periods until no longer infective, may yet retain agglutinating power for erythrocytes, but extracts of virus cause no agglutination. Study of the mechanism of this phenomenon may shed light on the way in which viruses infect cells. Apparently virus is adsorbed to erythrocytes, but after a period of time comes off again, is eluted, having during its attachment so altered the erythrocyte surface that the addition of fresh virus will no longer agglutinate the cells. Experiments with living ferret lungs (Hirst, 1943) indicated that virus was adsorbed to living susceptible cells just as to erythrocytes, but that spontaneous elution of virus did not occur: presumably the first attachment was succeeded by some other and firmer cell-virus relationship. On the other hand, in ferret lungs removed from the animal, virus was taken up, but later became detached, just as in tests with erythrocytes; the secondary stage, perhaps of penetration into the cell, seemed not to take place. Formalin-treated virus under these conditions was adsorbed, but could not be eluted.

Some other viruses, such as vaccinia, will agglutinate erythrocytes, but whereas influenza virus does so with cells of various animal species, vaccinia agglutinates only fowl-cells, but not the cells of every fowl (Clark & Nagler, 1943).

Interference Phenomenon

In some circumstances an animal cell may be simultaneously infected by two or more viruses, but such double infection is not always possible. There is evidence that sometimes, when a cell has sufficient contact with one sort of virus, it is for a time incapable of being infected with certain other viruses, which may be immunologically unrelated to the first. One virus is said to "interfere" with the action of another. The phenomenon is well known to students of plant viruses; as regards animal viruses it was first heard of (Hoskins, 1935) in connection with yellow fever; it was found that monkeys injected with the fatal viscerotropic strain of virus could have their lives saved by subcutaneous injection, at the same time or within a short period afterwards, of the neurotropic variant of yellow-fever virus. This variant does not kill monkeys when injected subcutaneously. Interference has been shown to occur between the viruses of yellow fever and Rift-Valley fever (Findlay & MacCallum, 1937a), between different strains of poliomyelitis (Jungeblut & Sanders, 1942), between different strains of influenza (Andrewes, 1942a; Henle & Henle, 1944), between the viruses of poliomyelitis and lymphocytic choriomeningitis (Dalldorf, Douglass & Robinson, 1938), between the viruses of western equine encephalomyelitis and St. Louis encephalitis (Duffy, 1944) and between two viruses affecting rabbits (Andrewes, 1940). The mechanism has been explained, at least in part, by experiments with two bacteriophages attacking *B. coli*. (There is every reason to consider phages as viruses which parasitize bacteria). Delbrück & Luria (1942) found that if even one phage particle had sufficient access to a bacterial cell, other phage particles of the same or another kind were frustrated in their efforts to infect the cell also. It was even found that phage inactivated by ultra-violet radiation could, after adsorption by the bacterium, still block the activity of other phage added later. The suggestion was made that the phage particle first added could preoccupy a key-enzyme in the bacterium, thus preventing the propagation of late-comers.

These findings have been followed up by Henle & Henle (1943, 1944) and by Ziegler & Horsfall (1944), who studied the power of one influenza virus to interfere with the multiplication of another within the allantoic cavity of chick-embryos; they also found that virus inactivated by ultra-violet radiation or otherwise could stop the activity of small quantities of living virus. All this work opens up new fields for thought and experiment. A new approach to the study of the mode of attack of viruses is clearly to be seen. The use of inactivated virus or attenuated live virus is now conceivable, not as an immunizing vaccine in the ordinary sense, but as an immediately effective prophylactic agent of a new type. Perhaps most entertaining of all are speculations as to whether one virus may fail to spread epidemically in a community because of the presence of another virus inimical to it.

Chemical and Physical Studies of Viruses

Our discovery of how viruses act will naturally be closely linked with the discovery of what viruses are. There are now available new tools with the aid of which we are learning more and more about their nature. Physical methods are not only revealing the size, shape and other properties of viruses, but are being used to purify them so that we may obtain some information as to their chemical composition.

The sizes of viruses have been estimated by filtration, centrifugation and optical methods, in most instances with fair agreement. The simplest, most generally used method is filtration through gradocol membranes. These are tough, opaque collodion membranes whose preparation was described by Elford (1931). The use of different proportions of solvents made it possible to prepare at will membranes with pores of any desired diameter, from 3μ or so downwards, and of satisfactory uniformity. From the results of filtration, it is possible to deduce the size of the virus-particles, but it is necessary for workers to be aware of the factors introduced by the nature of the suspending fluid, the titre of the unfiltered virus, and so on.

Many techniques have been described for determining the properties of viruses by ultracentrifugation. Most dramatic have been the results obtained with the Svedberg analytical ultracentrifuge and modifications of it. The rate of sedimentation of purified virus-suspensions is determined by means of photographs taken while the machine is actually running, but knowledge of shape and specific gravity is necessary before size can be deduced. Optical methods give the most direct information about size and shape. Ultra-violet photographs have revealed much, and the electron-microscope is showing us yet more, though the latter suffers from the disadvantage that material for study must be dried and examined *in vacuo*.

By the combined use of these new instruments we are now in a position to give approximate figures for the diameters of nearly all viruses, from the 10–15 $m\mu$ of poliomyelitis and foot-and-mouth disease viruses up to the 300 $m\mu$ (0.3 μ) of psittacosis. A virus related to poliomyelitis virus is now stated (Gard & Pedersen, 1941) to have an elongated needle-like shape—much as have tobacco-mosaic and other plant viruses; influenza virus is revealed by the electron-microscope to be oval or perhaps bean-shaped (Taylor, Sharp, Bland, Beard, Dingle & Feller, 1943); vaccinia and viruses related to it appear rectangular with areas of condensation of material within them, while others seem to be nearly spherical (Ruska, 1943; Rivers, 1943). Some bacteriophages have the appearance of rounded heads with slender tails attached—not unlike spermatozoa (Luria, Delbrück & Anderson, 1943).

Stanley's (1935) discovery that tobacco-mosaic could be crystallized gave the impetus to much work and to even more speculation as to what viruses were. So far no animal virus has been crystallized, though a number have been obtained in a state of considerable purity. The rabbit-papilloma virus (Bryan & Beard, 1940) seems to resemble many plant viruses in consisting, apparently, of pure nucleoprotein. Its simplicity of structure is also indicated by the fact that it behaves serologically as though consisting of a single antigen (Kidd, 1938). But most other animal viruses seem to be more complex. Vaccinia, for example (see Rivers, 1943), apparently has a surface-constituent which can become free and act as a soluble antigen, and so have several other viruses. That of vaccinia is itself complex, having a heat-stable and heat-labile constituent; moreover, vaccinia has probably got three or four other antigens in its constitution. Chemically, the virus contains nucleoprotein in which is incorporated a thymonucleic acid, and some lipid is apparently firmly bound in its structure. Copper and flavin are probably present also. Much work has been done in the effort to reveal enzymic activity on the part of purified vaccinia and other virus-particles, but the evidence is inconclusive, partly because enzymes from the host-cell seem to be rather easily adsorbed on to the surface of a virus. Few will now deny that vaccinia and other larger, relatively complex, viruses are analogous to bacteria, but have become simplified and have lost enzyme systems and other properties as a result of retrograde evolution and adaptation to a parasitic life. Not all are agreed, however, as to whether this explanation can still hold as one goes down the scale till one reaches the smallest, simplest viruses, including the plant viruses which can be crystallized.

Classification of Viruses

The time is not yet ripe to attempt a rigid classification of viruses, or to allot them generic and specific names. But it is worth considering briefly where to draw the dividing line between them and cultivable bacteria. No sharp line can be drawn by the application of any one criterion, whether this be size, shape, dependence for growth on living cells, staining properties or mode of transmission. But between the main body of viruses, which are clearly separate from bacteria, and the bacteria themselves, there stand two relatively well-defined groups:

(i) The *rickettsiae* which cause typhus and related diseases are smaller than most bacteria, nearly all completely dependent upon the interior of living cells for their livelihood, and their presence within cells at times leads to the formation therein of inclusion bodies. They differ from the majority of viruses in being relatively easily stained and in their varying morphology—bacillary forms are the general rule. All are insect-transmitted and most have an antigenic relationship to members of the proteus group of bacteria. Strong suspensions of some rickettsiae injected intraperitoneally into mice kill within a few hours by a kind of toxic action; but the "toxin" has not yet been separated from the living rickettsial bodies (Otto & Bickhardt, 1941). According to Zinsser & Schoenbach (1937), their metabolism in tissue-culture differs from that of viruses, but we have not yet sufficient information to say whether this is true. They are susceptible in some cases to chemotherapy but not by sulphonamides.

(ii) The "*LGV-psittacosis*" group has lately become defined mainly as a result of the work of Rake, Eaton and their collaborators (Rake, Eaton & Shaffer, 1941; Rake, Shaffer & Thygeson, 1942). It contains the viruses of lymphogranuloma venereum (LGV), psittacosis and related bird-borne infections (ornithosis; Meyer, 1942), trachoma, inclusion-conjunctivitis and pneumonia viruses affecting cats, mice and hamsters respectively. Viruses of this group have been recovered from a few cases of atypical pneumonia in man even in the absence of a history of contact with birds; the cause of the large majority of cases of "primary atypical pneumonia" is, however, obscure, though many claims to have recovered a virus have been published. Viruses of the "LGV" group are amongst the largest known; they stain, as do rickettsiae, with carbol-fuchsin by Machiavello's method and with Castañeda and Giemsa stains. They have a definite intracellular life-cycle, including large and small forms and morulae, as was first shown for psittacosis virus by Bedson & Bland (1934), but, unlike rickettsiae, they are at all stages rounded in shape. Like rickettsiae, the living virus-bodies injected in sufficient concentration kill mice by a quick toxin-like effect. All members of this group seem to be inter-related antigenically, as can be shown by cross-reactions in the complement-fixation test (Rake, Eaton & Shaffer, 1941). They can, however, be differentiated serologically when tests are made of the power of sera to neutralize the "toxin" (Rake & Jones, 1944). They differ from rickettsiae and from smaller viruses in that infections by many of the group can be favourably influenced by sulphonamides. They are not known to be insect-transmitted; but the agent of heart-water, which affects cattle in Africa, probably belongs to the group and is tick-transmitted; it has until lately been considered as a rickettsia.

Above these two groups stand the bacteria, whose properties need not be described except to point out that some of them are insect-transmitted, and some have not been grown *in vitro* on cell-free media. Below them are the other viruses, smaller in size, all obligate intracellular parasites, some of them insect-transmitted, of varying morphology, not so easily stained, not yet known to be susceptible to chemotherapy, many of them forming inclusion bodies within nucleus or cytoplasm, the smallest of them of relatively simple chemical composition. Viruses thus form a heterogeneous group and boundaries are nowhere easy to draw. But the writer finds it hard to agree with Rake that the "*LGV-psittacosis*" group should be excluded from the true viruses; it would seem more reasonable to include them and even the rickettsiae within the fold, though the latter are commonly considered as a group apart.

Chemotherapy of Virus Infections

It has been argued that the virus is a degraded bacterium, at its lowest reduced to naked nucleoprotein borrowing

enzymes for its metabolism from the cell it parasitizes (Laidlaw, 1938). If so, chemotherapy has a hard task to find a drug which will penetrate the living cell and there stop the activity of the intruder without at the same time damaging the life-processes of the host-cell. Nevertheless something can be achieved in this direction. The intracellular rickettsiae of typhus can be attacked with success in laboratory experiments, though no drug of clinical value has yet emerged. Activity has been described in such varied substances as sulphones (Andrewes, King, van den Ende & Walker, 1944), toluidin blue (Peterson, 1944) and penicillin (Moragues, Pinkerton & Greiff, 1944). The toluidin blue apparently has a direct action on the rickettsiae, while the sulphones have not. In the LGV-psittacosis group, lymphogranuloma venereum itself is favourably influenced by various sulphonamides (MacCallum & Findlay, 1938); so, too, are trachoma, inclusion-conjunctivitis, pneumonitis of mice and heart-water of cattle. Psittacosis, ornithosis and pneumonitis of cats are apparently unaffected (Rake & Hamre, 1944). At present only a few strains of each virus have been tested, and it remains to be seen whether within one sort of virus there may be differences in susceptibility, such as may be seen within the group of streptococci. It is not certain, for instance, that psittacosis is always resistant. A number of claims to have found chemotherapeutic remedies for other virus diseases have not been confirmed when adequate tests have been made, and we must admit that, at present, we are in sore need of something to indicate promising new lines of attack. The need is the greater as serotherapy has almost nothing to its credit in the field of virus diseases. Sero-prophylaxis, as used to abort or attenuate measles, is, of course, of established value.

Transmission and Epidemiology

Influenza: Aerial transmission of virus infections is now thought to be brought about not only through the agency of droplets as ordinarily conceived, but even more by droplet-nuclei in the sense of Wells & Wells (1936). The droplets ejected during sneezing and loud talking are thought to evaporate, before they can reach the ground, to particles of the order of size of 10μ or less, too small to be rapidly acted upon by gravity and, therefore, capable of remaining suspended in the air for many hours. Such minute particles in the form of artificial virus mists have been shown to be capable of infecting ferrets and mice with influenza; further, Andrewes & Glover (1941) adduced evidence that droplet-nuclei were probably concerned in the natural transmission of influenza infection from one ferret to another when the animals were placed in cages several feet apart. Much work is being done on methods of killing organisms in the air by means of ultra-violet radiation or chemical aerosols. These methods are most effective against droplet-nuclei, much less so against dust-borne particles; so it is important to know just how viruses are carried. Promising results have been reported in the control of measles and chicken-pox by the use of ultra-violet radiation in schools and institutions (Wells, Wells & Wilder, 1942; Barenberg, Greene, Greenspan & Greenberg, 1942), and of respiratory infections in a children's convalescent home by propylene glycol mists (Harris & Stokes, 1942). If such results are confirmed, their success will itself be evidence as to the route of transmission of these diseases. Haemolytic streptococcal infections seem to be carried especially by dust, and methods of air disinfection, apart from dust-control, are not so likely to be effective in such circumstances. Influenza virus can survive on dust (Edward, 1941) but we do not yet know whether this is of practical importance.

Two influenza viruses are known, A and B, and these are antigenically unrelated to each other. Within each virus-species are strains differing antigenically from each other in minor degrees. How far such minor differences affect the epidemiological picture we do not know. Outbreaks of A- and B-influenza occur at times together, but more often separately. B is not known to have caused a major outbreak in Britain; epidemics, since 1933, when the virus was discovered (Smith, Andrewes & Laidlaw, 1933), have all been due to A. In this country they have tended to occur every other year with the bigger epidemics only every fourth year; the sequence has become a little "out of step" since 1940. In North America and Argentina also a biennial outbreak has been the general rule. Laboratory workers have usually failed to obtain any evidence at all of the activity of A-viruses

in the 21 months or so between each period of activity, and it is of much importance for us to learn where it lies hidden in these periods. Shope (1941) has shown that, in the case of the closely related swine influenza, the virus may persist from year to year in the swine lung-worm. This has as its intermediate host the earthworm, and pigs at the beginning of a swine-influenza season may acquire infection by eating earthworms which carry lung-worms, these in turn bearing the virus infection. The story is rather more complex than there is space to describe now. A closely similar explanation is not readily conceivable in the case of the human disease, but we should be prepared for something bizarre to turn up. It has been suggested (Andrewes, 1942b) that between epidemics influenza virus may exist in human carriers, or as a cause of sporadic respiratory disease, but in a simpler "basic" form not recognizable by our present methods. Only at epidemic times would such a virus acquire, along with ability to spread in man, a pathogenicity for animals and ability to form in any quantity certain characteristic antigens. We have yet to explain, either along such lines, or by postulating yet undiscovered viruses C, D, E . . . , the frequent occurrence during A or B outbreaks, or separately, of many clinically similar cases, from which no virus can be recovered.

Poliomyelitis: The virus of infantile paralysis has been shown lately to be recoverable more easily from the faeces of patients than from nasopharyngeal washings (see Paul, 1941); it has also been found in sewage and on flies caught in the wild state (Trask, Paul & Melnick, 1943). The first portal of entry is doubtless the mouth and nose, but whether, therefrom, the virus commonly enters through the intestinal tract is still in dispute. It has been shown that poliomyelitis occurring in recently tonsillectomized children is more apt than ordinarily to be of the bulbar type (Aycock, 1942). Much interest has been aroused by the discovery of a biologically related virus (Theiler & Gard, 1940) which is present in the intestines and faeces of many normal laboratory mice. This only very exceptionally gives rise to spontaneous paralysis in mice which carry it, though it will readily do so on intracerebral inoculation. All these findings have caused us to re-orient our views as to the epidemiology and hygienic control of poliomyelitis.

Encephalitis: In the U.S.A., South America, Russia, and Japan, a number of forms of encephalitis have been recognized during the last decade; all transmitted by mosquitoes or ticks, and perhaps other arthropods. They are St. Louis encephalitis, Eastern, Western and Venezuelan equine encephalomyelitis, Japanese B encephalitis, Russian spring-summer encephalitis. Those named equine encephalomyelitis were so-called because of the losses they caused in horses, but they were later found to be causing disease in man, and also in birds. All the viruses concerned are of small size and readily transmitted to mice; there are antigenic relations between some of them, for example the St. Louis and Japanese B viruses (Casals, 1944). Insect-borne encephalitis in man has not been recognized in Britain, but should be watched for. Louping ill, which affects sheep in the hills along the Scottish border, is closely related to the Russian spring-summer encephalitis virus (Casals & Webster, 1944), and is known to be potentially pathogenic for man.

Vaccines

Few or no new principles have been established recently in the field of virus-vaccine prophylaxis. Living attenuated viruses are acknowledged to give the most durable immunity, but their uses for the control of human disease are few at the present time.

Vaccinia: The post-vaccinal encephalitis, which has been so troublesome, especially in the case of vaccination against smallpox, has been occurring much less frequently than a few years ago. We do not know why; its cause is still unsettled.

Yellow fever: The jaundice which followed vaccination against yellow fever with living attenuated virus in thousands of soldiers, especially in North America, has been a much more serious matter. Fortunately we do now know how to avoid that particular complication. An icterogenic agent was introduced in the human serum used for making or preserving the yellow-fever vaccine; the jaundice can be avoided by avoiding, as is readily possible, the use of serum in preparing the vaccine. This jaundice is but one example of "homologous serum jaundice," a disease most probably due

to a virus present in some apparently normal human sera. It has occurred following the injection of mumps or measles convalescent serum, or after transfusions. Its identity or otherwise with the common infectious hepatitis is much disputed; the infection has been transmitted to human volunteers, but not to any other animal species. MacCallum (1944)* has summarized the transmission experiments carried out up to the present.

Rabies: Webster (1939) has introduced improved methods for making and testing the inactivated vaccines used for immunizing dogs. He has also had the temerity (1942) to throw doubts on the efficacy of the time-honoured Pasteurian method of protecting by vaccination a person who has been bitten by a rabid dog; its reputation may, it is suggested, be due to the fact that only a small proportion of bitten persons would develop rabies in any case. With such a terrible disease, deliberate controlled experiments on man are hardly conceivable and one must seek for indirect evidence. If vaccination is as effective as has generally been believed, it is hard to explain why the time elapsing between the bite and the beginning of treatment seems not to affect the result. It would seem advisable to keep an open mind in this matter.

Measles has long baffled research workers because rhesus and other monkeys have been the only susceptible species and even they do not "take" regularly, perhaps because of some chance exposure of some shipments to infection. Several claims to have grown the virus on developing eggs have been made, and those of Rake & Shaffer (1940) seem to be well established. We may, therefore, at last have hopes of progress. After propagation through many generations on chorio-allantoic membranes of eggs, virus has successfully infected both rhesus monkeys and children. Further, the virus has apparently become attenuated so that it has been given to children as a living vaccine by atomizer into a sponge-bag face-mask (Stokes, O'Neil, Shaffer, Rake & Maris, 1943). Modified measles is thus produced in a majority of exposed children, but the reactions are admitted to be by no means negligible. Such children, subsequently exposed to natural measles, are said to have been substantially but by no means entirely protected. This work is in its early stages and will be followed with interest.

Influenza: We have long known (Smith, Andrewes & Laidlaw, 1935) that injection of formolized inactive influenza vaccines will immunize mice and ferrets against influenza, and produce an increase in specific antibodies in man. It has been another matter to prove their efficacy in protecting human beings against infection. One difficulty has been that the duration of increased resistance in man is almost certainly short, so that vaccination, to be effective, must be given shortly before an outbreak; and outbreaks have commonly failed to materialize at expected times. Further, clinical influenza comprises not only infections with the two known, and serologically distinct, viruses A and B, but other conditions of unknown cause giving rise to a similar clinical picture; this makes the evaluation of results a matter of much difficulty. Formolized vaccines have been made recently from embryonic fluids from infected eggs; a high titre of virus can be obtained in this way.

Trials made in the U.S.A. in 1941 gave conflicting results, which indicated at the best an apparent halving of incidence in the vaccinated (Horsfall, Lennette, Rickard & Hirst, 1941). In 1943, tests of vaccine gave decidedly better results (*Commission on Influenza, U.S. Army, 1944*); they were carried out in widely separated areas of the U.S.A., use being made of chick-embryo vaccine concentrated tenfold by adsorption on to chick erythrocytes and elution into a smaller volume of fluid (Francis & Salk, 1942). A reduction of between 3- and 4-fold in incidence was achieved. It may be that the use of better and more concentrated vaccine produced this encouraging result, but one suspects that a fortunate chance played a larger part: an epidemic of influenza A occurred in most of the vaccinated communities two or three weeks after the vaccinations, that is, at the time when protection should be maximal. Profitable future use of a vaccine may depend upon keeping an epidemiological watch on the doings of influenza viruses A and B, so that vaccine may be given at the optimum time and then only. It will certainly be useless to give vaccine to patients who "have influenza every year";

* [see also article by MacCallum and review of relevant papers, *BMB* 177-188]

their infections are most unlikely to be due to either virus. As to pandemic influenza, such as swept the world in 1918-19, nothing but the future can tell us whether such a visitation is

due to influenza A or B, to a mutant deriving from either of them, or to an unrelated virus; nor whether vaccines will be of any avail against so virulent a scourge.

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¹ [see BMB 65]

MODERN LABORATORY METHODS IN THE CONTROL OF TYPHOID AND PARATYPHOID-B FEVER

A. FELIX, D.Sc., F.R.S.

Emergency Public Health Laboratory Service

Two recently introduced laboratory methods have proved to be of great service to the epidemiologist who is called on to investigate outbreaks of enteric fever: (i) typing of typhoid and paratyphoid-B bacilli by means of Vi bacteriophage, and (ii) Vi-agglutination tests as an aid to the detection of chronic typhoid and paratyphoid-B carriers.

Typing of Typhoid Bacilli by the Vi Bacteriophage

Craigie & Yen (1938a, 1938b) made the important discovery that strains of the typhoid bacillus can be divided into a number of well-defined types according to their sensitivity to type-specific anti-Vi bacteriophages. Until then the typhoid bacillus had been regarded as a single species without varietal subdivision: It was known from the work of Hadley (1925-26), Burnet (1927, 1929) and Levine & Frisch

(1934) that the action of bacteriophages on the various *Salmonella* species is closely related to the presence of certain heat-stable "O" antigens in the bacterial cell.

As soon as the special importance of the so-called "Vi" antigen of the typhoid bacillus was recognized (Felix & Pitt, 1934) a number of investigators, working independently of each other in different countries, established the existence of bacteriophages that were specific for the Vi form of the typhoid bacillus (Sertic & Boulgakov, 1936; Scholtens, 1936; Craigie & Brandon, 1936). These phages attacked typhoid strains irrespective of their origin, provided that the cultures contained an adequate quantity of the Vi antigen.

The great advance due to the work of Craigie & Yen (1938a) was based on their observation of a special adaptability possessed by one particular anti-Vi phage. When this

phage was propagated on typhoid strains isolated from different outbreaks, preparations of bacteriophage were obtained which had developed a high degree of specificity for the particular strain on which they were grown. Strains that were related epidemiologically were invariably found to respond in an identical manner to the different phage preparations, and on this basis Craigie & Yen (1938b) identified a number of distinct Vi-phage types of *Bact. typhosum*. A small proportion of Vi cultures cannot be typed in this way, for reasons that are not yet understood. Such cultures are referred to as "imperfect" Vi forms.

The phage type of a strain is for all practical purposes a permanent character, and typing of the typhoid bacillus by this means gives results as reliable as those obtained in streptococcal or pneumococcal infections by the use of serological tests. It is thus possible to prove or disprove the connection between cases of typhoid fever occurring sporadically or during an outbreak, and between a carrier and the patients for whose infection the former is being held responsible.

It may be stated in passing that the Vi antigen of typhoid strains belonging to different phage types cannot be differentiated by any of the customary serological methods, including cross-agglutination and cross-absorption tests, and phagocytosis and passive-protection tests in mice (Felix & Pitt, unpublished results). It appears, therefore, safe to continue employing a single Vi + O strain of the typhoid bacillus for making typhoid vaccine or therapeutic anti-typhoid serum.

Practical Value of the Typing Method

The observations of Craigie and Yen on the epidemiological significance of Vi-phage types of typhoid bacilli have been amply corroborated. So far reports have been published from Canada (Brandon, 1940; Desranleau, 1942; Crossley, 1942), China (Yen, 1939), the United States of America (Lazarus, 1941; Coleman, 1942a), Great Britain (Felix, 1943; Bradley, 1943) and the Middle East (Boyd, 1943). The authors all agree that the bacteriophage test is a reliable guide to the epidemiological investigation of outbreaks or sporadic cases of typhoid fever.

In Britain the new method has been employed extensively since 1940. The Emergency Public Health Laboratory Service established a reference laboratory to which cultures of *Bact. typhosum* isolated in public health or clinical laboratories in any part of Britain have been submitted for typing by the bacteriophage technique. The application of the test has on many occasions proved to be of the greatest value to those concerned with the field investigations. In fact, the information derived from the typing of strains at a central reference laboratory often provided the only link between a number of widely scattered cases, and thus led to the detection of the responsible chronic carrier. The fascinating story of one of these investigations has been published by Bradley (1943). In this instance 23 apparently sporadic cases occurring in four counties and ten administrative districts, during the course of two years, were traced to a persistent carrier on a farm 100 miles away. Other striking examples of the value of the new typing method were encountered in localities varying from small rural districts to the metropolitan boroughs of London. These experiences led to the conclusion that phage typing is an indispensable aid to successful epidemiological field-work (Felix, 1943).

The standard phage preparations and standard type-cultures originally recommended by Craigie represented 18 Vi-types and subtypes. Subsequently a revised and simplified typing scheme was suggested by Craigie (1942), but his investigations regarding the required phage preparations have not yet been completed. Four additional Vi-phage types were identified in Britain (Felix, 1943); three of these are indigenous and the fourth may have been introduced from abroad. It is obvious that workers in different countries who are employing the bacteriophage typing method should maintain close contact and exchange cultures and phage preparations before types or subtypes are accepted as new and added to the original scheme of Craigie and Yen.

The following example illustrates the value of this kind of co-operation. In a small outbreak of typhoid fever in Britain, the cultures isolated from all the cases and from the responsible carrier were found to belong to a hitherto unknown Vi-phage type of the typhoid bacillus. The strain was provisionally labelled Type T. It was subsequently

learnt that the carrier had acquired the infection during the war in South Africa more than forty years ago, and it appeared probable that the strain was indigenous to South Africa. Cultures of this strain and the corresponding specific Vi-type phage were sent to Professor A. Pijper of the University of Pretoria; and Miss C. G. Crocker, who has had considerable experience of the phage-typing technique, soon reported that typhoid strains isolated early in 1944 from two patients in the Johannesburg district and from a patient in the Pretoria General Hospital belonged to Type T.

Typing of Paratyphoid-B Bacilli with the Vi Bacteriophage

In many countries, including Britain, paratyphoid-B fever is more prevalent than typhoid fever. It appeared, therefore, highly desirable to investigate the possibility of applying Vi-bacteriophage action to the examination of paratyphoid-B cases and carriers.

The presence in cultures of *Bact. paratyphosum* B of an antigen resembling the typhoid Vi antigen was described some years ago (Felix & Pitt, 1936), but most workers paid little attention to this finding. Later experiments carried out by Felix and Pitt before the war (but not yet published) strongly indicated that paratyphoid-B bacilli possess a heat-labile somatic antigen that is essentially similar to the typhoid Vi antigen, though differing from it in certain respects. This fact provided the theoretical basis of the investigations carried out in the Emergency Public Health Laboratory Service during 1941-43, which led to the recognition of anti-O and anti-Vi bacteriophages acting on *Bact. paratyphosum* B, and thus made it possible to apply the bacteriophage technique to the typing of paratyphoid-B bacilli (Felix & Callow, 1943).

Anti-O phages are very common and are readily grown from faeces, but they are non-specific. These phages attack not only paratyphoid-B bacilli but also many other *Salmonella* species which share the same O-antigenic components. On the other hand, the specific anti-Vi phages are rarely found in faeces, but they can be isolated from "lysogenic" rough variants or from phage-contaminated smooth cultures of the paratyphoid-B bacillus. Anti-Vi phages can be induced to develop a high degree of specificity for particular paratyphoid-B strains, whereas anti-O phages are incapable of such adaptation. By the use of four different preparations of adapted BVi phage, Felix and Callow evolved a typing scheme of paratyphoid-B bacilli which is almost identical with that which was first devised by Craigie and Yen for the typing of typhoid bacilli.

Only a small number (7%) of 714 strains isolated in all parts of Britain could not be typed by the four Vi-type phages originally used by Felix and Callow. In this respect the results with paratyphoid-B cultures were even more satisfactory than with typhoid cultures, for, in a series of 432 typhoid Vi strains, 15.9% were untypable with the 22 different Vi-phages employed. The number of known Vi-types and subtypes of the paratyphoid-B bacillus indigenous to Britain is now 5. It is, however, becoming apparent that hitherto unknown phage types are being introduced from abroad.

The epidemiological significance of paratyphoid-B Vi-phage types is the same as that of typhoid Vi-phage types. The first field inquiry, based on the results of the phage typing, into an outbreak of paratyphoid-B fever in a mixed urban and rural area was conducted during 1941 by the Ministry of Health in co-operation with the Emergency Public Health Laboratory Service, and clearly showed that there was complete harmony between the laboratory and the field findings (Hutchinson, 1943). A remarkable performance of the typing method was recently described by King (1944). It is the story of a symptomless carrier of paratyphoid-B bacilli of Type 3a, who had disappeared during an outbreak in 1941 but was re-discovered among the employees of a factory two years later when the sewage effluent was being examined for the presence of typhoid bacilli.

Detection of Chronic Typhoid and Paratyphoid-B Carriers with the aid of Vi-Agglutination Tests

i. *Chronic typhoid carriers*: The detection of a chronic carrier is usually a difficult task, though the methods of isolating typhoid and paratyphoid bacilli have been greatly improved through the introduction of refined culture media. The main difficulty is due to the fact that excretion is frequently intermittent, so that repeated examination of the excreta over a long period of time may be necessary.

Most workers now employ the test for the presence of typhoid Vi agglutinins as a preliminary screen for a suspected carrier. Since the test was first suggested by Felix, Krikorian & Reitler (1935) it has been used extensively in Britain (Felix, 1938a), South Africa (Pijper & Crocker, 1937a; 1937b; 1943), the United States of America (Eliot, 1940; Eliot & Cameron, 1941; Coleman, 1942b; Klein, 1943; Schlesinger, 1943), Italy (Giovanardi, 1936; 1937) and India (Bhatnagar, 1938; Bensted, 1940). These authors all agree on the usefulness of the test. Less favourable results were reported from the Sudan (Horgan & Drysdale, 1940) and Southern Rhodesia (Davis, 1940; Radovsky, 1942).

The practical value of the Vi-agglutination test is greatly enhanced by the fact that the reaction is independent of the intermittency in the excretion of bacilli. A few examples published recently may be quoted here. Schlesinger (1943) recorded the case of a woman from whom no fewer than 18 faecal specimens were negative, but continued search was encouraged by the presence of Vi agglutinins, and typhoid bacilli were isolated from bile and faeces after the injection of magnesium sulphate through a duodenal tube. Pijper & Crocker (1943) gave the history of a positive Vi-reactor in whose faeces typhoid bacilli were never demonstrated, though they were constantly present in discharges from a biliary fistula. Fry (1944) examined specimens of faeces from an intermittent excretor at weekly intervals over a period of 16 months. The specimens were examined on Wilson-Blair plates, and by subcultures on to Wilson-Blair medium after enrichment in both Müller's and Kauffmann's tetrathionate broth. Yet, of 80 specimens, only 22 were positive for *Bact. typhosum*. The longest negative interval was 9 successive weeks; if no enrichment media had been used, the longest negative interval would have been 27 weeks. Four tests for Vi agglutination which were carried out during this period gave the same result on each occasion, namely, a positive reaction at 1 in 20. At the post-mortem examination *Bact. typhosum* was isolated from the contents of the duodenum.

The technique of the Vi-agglutination test has been much simplified since preserved suspensions were adopted instead of living cultures (Felix, 1938b), and especially since the introduction of Bhatnagar's strain Vi I, which is a pure reagent for the demonstration of typhoid Vi agglutinins (Bhatnagar, Speechly & Singh, 1938). In Britain a standard agglutinable TVi suspension and a standard agglutinating TVi serum are available through the Standards Laboratory (*Medical Research Council*), Oxford, and are strongly recommended for general use.

The frequency of a positive Vi reaction in chronic typhoid carriers is remarkably high. From my experience over a period of nearly ten years it would appear that not more than 5% to 10% of true chronic carriers will give a negative Vi reaction. When the carrier condition has lasted for a very long time, for example, periods of 30 or 40 or more years,

the power of producing Vi antibody often tends to be exhausted.

The Vi test can also be used for the detection among recovered typhoid patients of those who are likely to become chronic carriers. The customary three negative examinations of the excreta are no guarantee that potential chronic carriers are not discharged from hospital. Such carriers can be detected by two tests for Vi agglutination, the first carried out on the eve of discharge from hospital, the second after an interval of about six weeks. A steady or rising Vi-titre will arouse suspicion as to a possible chronic carrier condition, a decreasing Vi-titre or a negative Vi reaction will indicate freedom from infection. The follow-up of recovered patients in this way seems to make it possible in time to eradicate typhoid fever completely.

ii. *Chronic paratyphoid-B carriers*: It is generally believed that the Vi-agglutination test is applicable only to typhoid and not to paratyphoid carriers. Unpublished investigations carried out by the writer in the Emergency Public Health Laboratory Service during the present war have shown that the method can be applied successfully to the examination of paratyphoid-B carriers as well. The Vi test, however, is more complicated in paratyphoid-B than in typhoid, since a "pure" Vi variant of *Bact. paratyphosum* B, comparable to Bhatnagar's typhoid strain Vi I, has not yet been isolated. When a serum is tested for Vi antibody to paratyphoid-B bacilli, its O-antibody content must, therefore, first be completely removed by absorption with a pure O culture. Most of the chronic paratyphoid-B carriers that have been examined so far gave a positive BVi reaction, but the frequency of a positive reaction in paratyphoid B is not as high as that of a positive TVi reaction in typhoid carriers.

The proportion of mild and symptomless cases is very much greater in paratyphoid B than in typhoid fever, and one of the difficulties that often arises in the course of an epidemiological investigation is the question whether a person who has been found excreting paratyphoid-B bacilli is a true chronic carrier or a temporary excretor following a mild or symptomless infection. The former may be the original source of the outbreak, whereas the latter is merely one of its victims, though he, or she, may have been responsible for the spread of the infection. In all the recent outbreaks of paratyphoid-B fever in Britain, the persons identified as responsible for the spread of infection were later proved to be temporary excretors. The true culprits, namely the chronic carriers, escaped detection. In the diagnosis of the true carrier the final verdict depends on the result of the bacteriological examination of the excreta, which must be continued for not less than a year, but useful information is often obtained much sooner from two or three examinations of the blood serum at intervals of about six weeks. A decreasing BVi titre will indicate temporary excretion, whereas a steady or rising titre will arouse the suspicion that the person has been or is likely to become a chronic carrier of the infection.

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¹ [see BMB 70]
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HOSPITAL INFECTION: A HISTORICAL REVIEW

ROBERT CRUICKSHANK, M.D., M.R.C.P., D.P.H.

London County Council Group Laboratory, North-Western Hospital, Hampstead

Any congregation of people increases the chances for the spread of infection. Thus it is that towns, gaols, ships, barracks, schools, and even hospitals, have from time immemorial been the breeding ground of epidemics, or as Greenwood (1935) has aptly called them, "crowd diseases". That hospitals designed for healing the sick should, from their very nature, carry some added danger to those who require their healing aid has long worried the hospital administrator. As that greatest of hospital reformers, Florence Nightingale, has said, "it may seem a strange principle to enunciate that the very first requirement in a hospital is that it should do the sick no harm". To-day the problem of hospital infection, although less serious and different in kind from that experienced before the Listerian era, still remains unsolved and, in recent years, has stimulated much research directed towards its control and elimination. In the past century British workers have played a large part in unravelling the intricacies of this complex problem.

Hospital Infection in the 19th Century

Before Lister demonstrated the part that bacteria play in the production of wound-infection, the surgical wards of most hospitals were filled with patients whose wounds, whether accidental or intentional, almost always became septic, so that healing, when it occurred, was by granulation or scabbing. Unfortunately the sepsis spread beyond the local wound in many cases, and more generalized infections, such as erysipelas and cellulitis, pyaemia, septicaemia and hospital gangrene, were common complications of any wound. The first three of these generalized infections would be recognized to-day as streptococcal or staphylococcal in aetiology: the bacteriology of hospital gangrene—described by Cameron¹ (1907) as a progressive mortification of the tissues adjacent to the wound and apparently infectious—cannot be established, as it is doubtful whether anything comparable to it now exists. The result of the gross wound-sepsis was a high morbidity- and mortality-rate among surgical patients; for example, practically all cases of compound fracture became infected and 25% to 50% of them died. Because the constitutional disturbance accompanying the wound infection affected the patient's appetite, a light diet, low in calories, was always prescribed. This light hospital diet was continued as a routine long after the need for it ceased to exist, and only to-day is it being realized that "hospital diet" is quite inadequate for the needs of most patients. The wards themselves had constantly a characteristic sickly odour, and surgery was confined to a limited field—about one-fifth of the operations were amputations—largely because surgeons feared for the outcome of more venturesome interference. The surgical wards of most hospitals acquired an evil reputation, and as the results of operative procedures were so much better when carried out in private houses, many doctors preferred to bring the surgeon to the patient rather than the reverse. Even as late as 30 years ago, I remember as a boy how in country districts the surgeon frequently came to operate, often under great difficulties, in a private house because of the countryman's fear of going to the infirmary. No wonder that certain hospital authorities felt impelled to destroy the hospitals and build anew.

If surgical wards had the worst reputation they were not alone in fostering secondary infection. In a careful and penetrating analysis of mortality-rates in maternity hospitals, Florence Nightingale showed that many of these institutions had bad records of puerperal sepsis with "blood-poisoning" as a frequent complication, and with maternal mortality-rates as much as 7 times as high as those occurring in domiciliary practice. The effect of overcrowding, of large undivided wards and poor ventilation, in encouraging outbreaks

of puerperal sepsis in these institutions was recognized by her, and the infectiousness of the condition was admitted, although she was apparently unaware of the earlier researches of Semmelweis on the control of the manual transference of infection by hand-washing in "chlorine-water".

Earlier, Miss Nightingale, as a result of her unique experience in the Crimean War, where, incidentally, 2 out of every 5 patients admitted to the large general hospital at Scutari died, had drawn attention in forceful language to the unsatisfactory design and management of hospitals, and had indicted agglomeration of a large number of sick under one roof, deficiency of space, deficiency of ventilation, and deficiency of light, as the principal factors predisposing to hospital infection and the unsatisfactory results of hospital treatment. In children's hospitals, conditions were even worse. Throughout Europe, till late in the 19th century, mortality-rates in children's hospitals were excessively high, and parents feared to send their children to these institutions, "where they died not from the malady for which they entered the hospital, but from that which they contracted therein". Thus hospital infection played havoc among medical as well as surgical patients. No doubt also the great increase in urban populations associated with the industrial revolution in the 19th century helped to overcrowd hospitals that were very inadequately staffed and equipped, and we know to-day these are among the most important factors contributing to cross-infection in hospital.

One cannot close this grim chapter without paying a tribute to Florence Nightingale who in three slim volumes *Notes on hospitals* (1859), *Notes on nursing* (1860), and *On lying-in institutions* (1871) had shown how well she comprehended the root causes of hospital infection, and had enunciated the principles of good hospital design and management, and what is even more important, of good nursing. It is particularly interesting at the present time to note that she was a strong advocate of damp-dusting and -sweeping for getting rid of dust, for as she said "air can be soiled just like water".

Listerian Principles

Pasteur's demonstration of the bacterial origin of fermentation was the stimulus which inspired Lister (see Godlee, 1917) to devise methods for preventing infection of wounds in his surgical wards. Believing that bacteria causing "putrefaction," or sepsis as we should now call it, came from a variety of sources outside the body (and at that time he naturally thought that any extraneous micro-organism was pyogenic), Lister introduced antiseptics to prevent access of these bacteria from hands, instruments, dust, air, etc., to open wounds—e.g. compound fractures, incised abscesses which in those days were mostly tuberculous, and intentional wounds. Carbolic acid had been used as a disinfectant for sewage,¹ and Lister employed it in a variety of forms: first as the crude undiluted fluid; as a 1:20 solution of phenol crystals; as a 1:5 solution in oil, made into a putty; as a mixture of phenol in shellac spread on calico; and finally as an antiseptic gauze.

Later, probably impressed by Tyndall's (1881) work on the pollution of the atmosphere with particulate matter, Lister advocated the use of the carbolic spray for preventing access of air-borne bacteria to the wound, but after some years' experience of this method he became persuaded of its uselessness, since bacteria in the atmosphere seemed to have little pathogenicity. Lister knew that carbolic acid was harmful to tissues, but its caustic action seemed a low price to pay for preventing infection and saving many lives from the terrors of septicaemia and hospital gangrene. It is perhaps apposite to remark here that proflavine, one of the most useful of modern antiseptics for the treatment of war wounds, is also a tissue poison. The important point to note in Lister's work is that for the first time *an effective barrier had been imposed between infecting organism and susceptible tissue.*

¹ [Sir Hector Cameron was the pupil and personal friend of Lord Lister and in his small book *On the evolution of wound treatment during the last forty years* he traces the development of modern surgery from Lister's antiseptic methods.]

¹ [Lemaire's use of carbolic acid in France was not known to Lister until 1867.]

There were many contemporary critics of Lister's antiseptic surgery, but the criticisms were mainly of the methods employed, and not of the principles which constituted the first premeditated step in the control of hospital infection. The dramatic results can best be recorded in Lister's own words in 1867:

"But since the antiseptic treatment has been brought into full operation, and wounds and abscesses no longer poison the atmosphere with putrid exhalations, my wards, though in other respects under precisely the same circumstances as before, have completely changed their character; so that during the last nine months not a single instance of pyaemia, hospital gangrene, or erysipelas has occurred in them.

"As there appears to be no doubt regarding the cause of this change, the importance of the fact can hardly be exaggerated."

And in a letter to his father in the same year he remarked:

"I now perform an operation for the removal of a tumour, etc., with a totally different feeling from what I used to have; in fact, surgery is becoming a different thing altogether."

From antiseptic surgery there gradually evolved the elaborate ritual of aseptic surgery dependent mainly on sterilization by heat. While sufficiently adequate for the deliberate surgery of peace-time, the aseptic technique, as we shall see later, may fail in the face of the more exacting conditions of war.

Cross-infection in Paediatric and Isolation Hospitals

As the beneficial effects of antiseptic surgery gradually became accepted, those in charge of medical patients, and in particular of children's hospitals, began to realize that there was an urgent need for medical as well as surgical antiseptics. The criticisms of Florence Nightingale had already done much to restrict overcrowding and improve ventilation, but mortality rates in children's hospitals were still, in the latter half of last century, 20% to 40% of all admissions. However, the decade between 1880 and 1890 saw bacteriology established as a new science, the infectivity of many diseases was becoming accepted, and experiments were already being made on the mode of transference of the infectious agents. The first specific measures aimed at reducing cross-infection in medical wards were carried out by Grancher and Hutinel around 1890 (Grancher, 1888; Hutinel, 1894) in two children's hospitals in Paris. In these hospitals, patients with diphtheria, scarlet fever and measles were being nursed beside non-infective patients, and the case-mortality of, for example, measles ranged from 40% to 50%. Among the measures introduced by Hutinel at the *Hospice des Enfants Assistés* were: disinfection of linen; thorough cleansing of wards every two weeks; examination of all new admissions for sore throat, etc.; strict isolation of cases of diphtheria and other infectious diseases; subdivision of large wards into "boxes" for one or two beds where patients with bronchopneumonia, peritonitis, diarrhoea, syphilis, etc., could be isolated; use of holland overalls by nurses and doctors; and washing of hands with antiseptics.

A little later the work of Flügge and his pupils (1897, 1899) showing that infective droplets expelled by tuberculous patients during coughing had a limited range of about 3 feet [about 1 m.], and that guinea-pigs could be infected much more easily by direct exposure to a tuberculous patient than by inhalation of dried infected sputum, led to the doctrine of the spray or droplet spread of respiratory diseases with its implication of transference only by close contact, instead of an aerial spread, for which Power (1880-81) from his studies on the epidemiology of smallpox had been such a strong advocate. Thus, instead of complete wooden barriers, Grancher later used screens around individual patients. Everything used by each patient was kept separate, and crockery, etc. was always boiled after use. As a result of this technique he claimed that secondary cases of measles were reduced by two-thirds, while those of scarlet fever and diphtheria were reduced from about 24 to nil per annum. The system of cubicle-isolation with incomplete partitions was introduced into Britain in 1906 by Pugh, who found that only measles and chicken-pox among the specific fevers were resistant to this method of controlling hospital infection. Instead of visible barriers, such as partitions or screens. Crookshank (1910) introduced a technique for nursing infectious patients by "barrier" for single patients and "bed-isolation" for all patients in the ward. Essentially this technique involved strict precautionary measures by

trained nursing staff to prevent the spread, manually or by ward equipment, of infectious material from the isolated patient to his neighbours. The bed-isolation technique was put to the test in two small wards by Rundle & Burton (1912) who, over a period of 2 years, nursed 473 patients suffering from a variety of diseases (puerperal fever, erysipelas, pertussis, chickenpox, rubella, doubtful scarlet fever and diphtheria, convalescent measles) with only two secondary cases of scarlet fever. Thus the success of the bed-isolation technique supported Flügge's teaching and demonstrated the important part which the hands may play in the transference of infection (see Harries, 1935). Meanwhile the advent of the 1914-18 war was to upset the complacency of surgeons who had come to believe that aseptic surgery was sufficient to control the spread of infection in surgical wards.

Hospital Infection of Open Wounds

Although in the 1914-18 war the incidence of obvious infection was, apart from gas gangrene, insignificant among wounded soldiers on admission to hospital, surgeons soon became depressed at the high proportion of wounds which subsequently became septic or were complicated by spreading cellulitis, osteomyelitis, pyaemia and septicaemia. It was almost akin to pre-Listerian days, and the aseptic technique seemed powerless to prevent this gross wound sepsis. Bacteriological examination showed that less than 20% of the wounds yielded *Strept. pyogenes* or *Staph. aureus* on arrival at the casualty clearing station or base hospital, whereas some 80% to 90% were infected with the streptococcus 2 weeks after admission to hospital (Stokes & Tytler, 1918; Fleming & Porteous, 1919). The trouble was, of course, that war wounds could not be closed by primary suture, and there was therefore a great agglomeration of patients with open wounds, susceptible to infection and frequently exposed to the risk during the daily dressing. The obviously infected cases with purulent discharge or persistent sinuses remained for weeks or months in the wards and constituted a heavy load of infection from which newly-admitted patients could scarcely avoid becoming in turn infected.

There was a renewal of interest in antiseptic surgery and a great stimulus to the production of new antiseptics. Outstanding among these were: the aminoacridine compounds or "flavines" introduced for this purpose by Browning and his colleagues (see Browning, 1943) which had the advantage over older antiseptics of having little toxicity for tissues and being unaffected by mixture with serum; and the hypochlorites, e.g. eusol (Smith, Drennan, Rettie & Campbell, 1915; Smith, Ritchie & Rettie, 1917), with their cleansing effect on discharging surfaces, although they rapidly became inert and had to be frequently renewed, as in the Carrel-Dakin method of irrigation. If these new antiseptics had considerable advantages over Lister's carbolic acid, the Listerian principle of preventing access of pathogenic bacteria to the wound was often forgotten, and antiseptics were usually applied after sepsis had already declared itself clinically. Pus interferes with the action of most antiseptics, and the views of surgeons about the efficacy of local antiseptics were by no means unanimously favourable. With the return of peace-time surgery, the need for antiseptic dressings was greatly reduced, and although eusol and the flavines still enjoyed a certain popularity the stimulus of necessity for the discovery of new and better antiseptics was lacking.¹

Although surgeons had gone back with a sigh of relief to aseptic surgery, those responsible for the treatment of patients with burns or with disease of the ear, nose and throat could not fail to be impressed by the frequency of infection among such patients. For example, pyrexia commencing on the second or third day and continuing for a week was a common feature in burns of the second or third degree, while "clean" operations, e.g. for cleft palate in otorhinological wards, frequently failed to achieve the desired result because of secondary infection.

An investigation of the bacteriology of burns (Cruikshank, 1935) showed that while 11% of newly-admitted patients

¹ [The status and relative merits of local antiseptics at the beginning of the present war has been well summarized by Garrod in the *Lancet's* "War primer on wound infection" (1940). See also *BMJ* 48, a review (1943) of recent advances in the antiseptic treatment of wounds, by the same author.]

yielded scanty haemolytic streptococci from the burnt surface, within 3 to 6 days 66% were grossly infected with the haemolytic streptococcus, while 2 out of every 100 patients developed scarlet fever, and sore throats and septic fingers were unduly prevalent among the nursing staff. Haemolytic streptococci were found in considerable numbers in the air and dust of the burns wards, but rarely in general surgical wards and not at all in medical wards. In the previous year Griffith (1934) had, after much painstaking research, published his classical work on the serological division into a large number of types of the haemolytic streptococci responsible for human infections. The application of his technique to the burns streptococci showed that one particular type of streptococcus was present in a number of infected burns in the same ward. This was the first piece of circumstantial evidence indicating that spread of the haemolytic streptococcus from infected to uninfected wounds was occurring, and that infected dust was a possible mode of transference of the organism. In 1936, Okell & Elliott reported 14 outbreaks of streptococcal cross-infection during 3½ years in 4 small otorhinological wards, the secondary infection varying from pharyngitis, otitis, mastoiditis, adenitis, to erysipelas, scarlet fever, bronchopneumonia and septicaemia. The adoption of a modified bed-isolation technique carried out with care and intelligence by an instructed nursing and medical staff considerably reduced the incidence of cross-infection in their wards.

In the present war, the occurrence of secondary hospital infection of open wounds has been amply confirmed by Miles and his colleagues (1940), using repeated swabbings and serological typing of the streptococcus as detective devices. The conditions of war make it very difficult to avoid infection of wounds, and, despite the introduction of a "no-touch technique," and the prophylactic use of sulphamides, both locally and by mouth, war-wound sepsis is still a great menace. Antiseptics have come into fashion again, and each new preparation is hailed as the answer to the surgeon's prayer. Among antiseptics that have proved their worth in controlling wound sepsis in recent years are 1% proflavine powder (Mitchell & Buttle, 1942); a sulphathiazole-proflavine powder in the proportion of 99:1 and a total dosage of 10-15 g. (McIntosh & Selbie, 1944); propamide¹; and, of course, penicillin in solution, powder or cream.² However, it must not be forgotten that radical surgery with thorough excision of any lacerated wound or necrotic tissue is a prime necessity in dealing with war wounds, while sufficient emphasis is still not given to the Listerian principle of prophylactic antiseptics.

Air-Borne Infection³

Although Flüge's doctrine that most respiratory diseases are conveyed by spray or droplet, requiring close contact between infected and susceptible persons, has long been generally accepted by clinicians, the possibility of the transmission of infection by air is no new conception. Apart from theories about miasma, it is nearly half a century since Washbourn & Eyre (1902) showed that living pneumococci could be isolated from the dust of ward and laboratory, and about the same time German workers carried out a large series of tests demonstrating the prolonged viability of naturally dried pathogens, such as the diphtheria and tubercle bacilli, the streptococcus and staphylococcus. However, despite the evidence (see Thomson, 1916) that the infecting agents of chickenpox and measles could be carried considerable distances, it is only in recent years that the importance of "air-borne" infection has again come into prominence.

Droplet-nuclei. Renewed interest in the possibility of an aerial spread of infection was stimulated by the work in America of Wells and his associates (see Wells & Wells, 1936), who showed that droplets expelled during talking, coughing and sneezing do not *all* fall to the ground within a few feet of the individual, but that instead, droplets of less than 0.1 mm. diameter, called by Wells droplet-nuclei, are so light, or become so by evaporation, that they remain suspended in

the air like particles of smoke and may be carried considerable distances by air-currents.

Precise data on the fate of expelled droplets have recently been recorded by Bourdillon & Lidwell (1941) using flash photography. When a patient with a respiratory infection coughs or sneezes, the majority of the droplets describe a curved trajectory to the ground within a radius of 4 to 6 feet [about 1-2 m.] (see also Hare, 1940), so that a susceptible person would have to stand in very close proximity to be directly infected by these coarser droplets. The smallest droplets remain suspended in the air for periods of 30 minutes or more, and although dispersion of these droplet-nuclei by air-currents must mean a great dilution of the *materies morbi*, epidemiological evidence indicates that in many virus diseases the infecting dose is very small. Thus an aerial carriage of droplet-nuclei would help to explain the high infectivity of such infections as smallpox, chicken-pox, measles, and dog distemper (see Dunkin & Laidlaw, 1926). Andrewes & Glover (1941) showed that influenza virus could spread from one ferret-cage to another along an S- or U-shaped duct, allowing the passage only of droplet-nuclei or very fine dust.

Dust-borne infection. Meanwhile, the larger expelled droplets have fallen to the ground or on to bed-clothes and become dried. If they contain bacteria that withstand natural drying, as is the case with many respiratory pathogens, they infect the dust on the floor and the fluff of the bed-clothes. Ward activities, in particular sweeping, dusting and bed-making, raise these infective particles into the air, so that during bed-making in a scarlet-fever ward a patient may inhale 100 to 200 dried haemolytic streptococci. Yet clinicians have been unwilling to believe that these dried and possibly "emasculated" bacteria could overcome the natural resistance of tissues and initiate infection. However, strong circumstantial evidence in favour of dust-borne infection has been provided by:

- i. The occurrence of tonsillitis due to a particular type of streptococcus in an individual who swept out a cubicle vacated 3 days earlier by a puerperal patient infected with the same serological type of streptococcus (White, 1936).
- ii. Two small outbreaks of puerperal sepsis where direct transference by human carriers seemed to be excluded (Cruickshank & Godber 1939).
- iii. The occurrence of an explosive outbreak of streptococcal infection following influenza (Cruickshank & Muir 1940).
- iv. The control of secondary streptococcal infection among children in a measles ward by preventing dissemination of infected dust (Wright, Cruickshank & Gunn, 1944).

Additional supportive evidence was the finding by Brown & Allison (1937) of haemolytic streptococci in considerable numbers in the air of scarlet-fever wards of the same serological types as were found in the upper air passages of the patients. These two workers had earlier (1937) shown that most of the complications of scarlet fever in hospital patients were due to cross-infection with serological types of the streptococcus other than that causing the original disease. Their findings were fully confirmed by de Waal (1940). The demonstration by Anderson, McLeod and colleagues (1931, 1933) of three biological types of the diphtheria bacillus called by them *gravis*, *intermedius* and *mitis*, afforded them the opportunity to prove that cross-infection was a frequent, if clinically insignificant, occurrence in diphtheria wards. Later Crosbie & Wright (1941) and Wright, Shone & Tucker (1941) showed that infected dust was almost certainly one of the vehicles which facilitated diphtheritic cross-infection. Among virus diseases, psittacosis has been acquired by attendants from the sweepings of parrot cages (McCoy, 1934), while evidence of air- and dust-borne rickettsial infection, e.g. typhus (van den Ende, Harries, Stuart-Harris, Steigman & Cruickshank, 1943) and Q fever (Hornibrook, Nelson, Dyer, Topping & Bengtson, 1940) has also recently been recorded.

Methods of control. The methods—chemical and physical disinfection of the air, dust-suppressive measures—for dealing with air-borne infection are discussed by Professor Miles on another page.¹ All that need be said here is that much work has been done in Britain in the development of these methods. Thus, Douglas, Hill & Smith used hypochlorite sprays for

¹ [see BMB 48 & 58]

² [see BMB 197-238]

³ ["Air-borne infection" is used here to mean the transference of infection through the air other than by direct "droplet" infection which requires close contact between infector and infected (Cruickshank, 1940).]

¹ [see BMB 554]

aerial disinfection as early as 1928, and Masterman (1938) developed the technique and enunciated the principles of disinfection by hypochlorite, which he maintained acted in virtue of the formation of hypochlorous acid gas. His work has been confirmed by Edward & Lidwell (1943) and the principle of aerial disinfection by vaporization of suitable substances which saturate the air and condense on bacteria-carrying particles has now become generally accepted (see Robertson, 1942). A great volume of research, much of it unpublished, on the problems of aerial disinfection has been carried out by teams of workers at the National Institute for Medical Research, London. Some of their earlier findings have been summarized by Andrewes (1940). Twort and his colleagues at Portslade (Twort, Baker, Finn & Powell, 1940; Baker & Twort, 1941; Twort & Baker, 1942) have also made valuable contributions to the subject.

Dust-suppressive measures have been developed by van den Ende and his colleagues (1940, 1941a, 1941b) by the utilization of certain oils, e.g. crude paraffin oil and "technical white oil," for application to floors and to bed-linen. The value of such measures has been well demonstrated by the reduction of secondary bacterial infection in measles wards (Wright, Cruickshank & Gunn, 1944), of cross-infection in scarlet-fever wards (unpublished observations) and of upper respiratory infections among troops in training units (Thomas, 1941; Anderson, Buchanan & MacPartland, 1944). The oiling of bed-linen in hospital laundries is now a practical possibility (Harwood, Powney & Edwards, 1944).

Enthusiasm for these new methods of cleansing the air must not blind us to the paramount value of adequate ventilation, particularly in winter, in the control of air-borne infection. To quote Florence Nightingale again "windows were made to be opened and doors to be shut," and patients in bed are remarkably tolerant of cold. Proper bed-spacing, i.e. 144 square feet [about 13 m.²] per bed in infectious diseases hospitals and at least 100 square feet in children's and maternity hospitals, must also be maintained, for overcrowding increases the risk of cross-infection which, in turn, entails a longer stay in hospital and a slower turnover of patients, thus defeating the objective which prompted the increase in beds. Hospital wards should also be well-lit for, besides the bactericidal action of direct sunlight and daylight, Garrod (1944) has recently shown that daylight through ordinary glass is also bactericidal. Thus it is that, in the summer months with better ventilation, more daylight and less overcrowding, the incidence of respiratory cross-infection is always at its lowest. Our aim must be to utilize all the available methods of control in order to keep air-borne infection in hospitals at the same low level in both summer and winter.

Hospital Infection To-day

Advances in our knowledge of the mode of spread of infection, due in large part to laboratory research, have altered considerably the present-day conception of hospital infection. In particular, recognition of the human carrier

as a reservoir of infection has helped to explain many anomalies and to dispel old notions about the dangers of miasma, sewer gases and the like. Hospital infection could to-day be defined *clinically* as manifest respiratory, gastro-intestinal, wound, skin, or mucous membrane infection, arising during the course of another disease, and, *bacteriologically*, as the acquisition by a patient of pathogenic organisms not present on admission.

If, with modern improvements in technique and accommodation, clinicians feel that cross-infection is no longer a serious problem, they may be reminded of such recent happenings as a secondary streptococcal infection-rate of over 70% in measles wards with one-fifth of the children developing otitis media (Wright, Cruickshank & Gunn, 1944); more than 60% of the clinical complications in scarlet fever due to cross-infection with an average stay in hospital of 52 days compared with 27 days for uncomplicated cases (de Waal, 1940); 13% of 551 children cross-infected with the haemolytic streptococcus during one year's admissions to a children's department (J. Wright, 1940); outbreaks of neo-natal diarrhoea with mortality-rates of over 50% (Ormiston, 1941; Sakula, 1943); and the all-too-frequent pyogenic infection of wounds in burns and otorhinological wards. Gastro-enteritis, dysentery, pemphigus neonatorum, diphtheria, are other hospital infections which are still too common.

Accompanying, and far transcending the obvious clinical infection, is the latent bacteriological infection serving as an undetected reservoir for the infection of new and susceptible cases. Thus, cross-infection may be likened to an iceberg with but one-ninth of its bulk above the surface for all to see. It is the submerged eight-ninths that spells danger, and it is the function of the bacteriologist to unmask this hidden infection in throat, gut or wound, for it is the unknown, not the known, carrier of pathogenic organisms who is most likely to be a danger to his fellows. This modern concept of hospital infection is developed in a recent *Medical Research Council War Memorandum* (1944), which discusses the sources and modes of spread and the general measures for prevention of hospital infection, gives specific advice about the control of contact and mediate, droplet and air-borne infection, and recommends procedure when a particular type of infection occurs in a ward. This practical pamphlet should be read by all who are interested or concerned in the problem of hospital infection, for only by intelligent and whole-hearted co-operation by everybody, from physician and surgeon to porter and domestic, can hospitals be made safer for those who require their healing aid. The complex problem of cross-infection is still unsolved, but to-day we understand more clearly what the contributory factors are. We still do not know the relative importance of better hospital design and equipment, well-trained nursing staff, new methods for controlling air-borne infection, chemotherapy and chemoprophylaxis, but if we apply the knowledge we already have we shall have gone a long way towards achieving Florence Nightingale's first requirement in a hospital that it should do the sick no harm.

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554

OBSERVATIONS ON THE CONTROL OF HOSPITAL INFECTION

A. A. MILES, F.R.C.P.

Professor of Bacteriology, University College Hospital Medical School

The problems of hospital infection are like the problems of transmissible disease in general; they cannot be appreciated without a knowledge of the reservoirs of infection, of the channels whereby the infective agents reach the susceptible person, and of the mode of infection. The hospital problem is peculiarly acute in that a large variety of infections may be gathered together in one institution, and that infected and susceptible persons are, geographically speaking, crowded together in a small area. Moreover, the infected, because they are ill enough to require hospital treatment, are likely to be heavily infected, and the susceptible, being treated for other, perhaps debilitating, diseases, are likely to be more susceptible than healthy persons in the population at large. These epidemiological disadvantages of hospitals are of course counter-balanced by the advantages of supervision of the hospital community by skilled medical staff. But though in the past century the reforms of hospital administration and technique have eliminated the grosser horrors of hospital infection, it is not fully recognized to-day that, even in modern hospitals, infection of this sort frequently occurs, and that in many hospitals the preventive measures in force would prove inadequate to prevent the spread of an infection among the patients or staff, if an infective agent were introduced among them.

Added Infection: Magnitude of the Problem

The infections with which we are concerned are qualified by the word "hospital," which is intended to indicate, not that they are necessarily acquired in a given type of institution, but that they are acquired by a patient as a result of submitting to any form of medical or surgical treatment. The word "hospital" is too restricted; the important feature of the infection is that it is *added* to a patient already suffering from the disease for which he seeks treatment. In this article, "added infection" is used synonymously with "hospital infection," and is preferred, because it keeps clearly before the reader the idea of an unnecessary and to a large extent an avoidable burden imposed on the patient.

It is often assumed that the risk of added infection is adequately met if the great majority of patients never suffer from a severe disease traceable to an infection picked up in the hospital. This is erroneous for a number of reasons. In the first place, the sources of infection may be absent or scanty for long periods, and the precautions, though poor, are consequently never tested against a heavy load of infection. For instance, in surgical wards, the incidence of infection in "clean" operation wounds rises in war-time, when patients with such wounds are nursed alongside patients with heavily infected war-wounds (McKissock, Wright & Miles, 1941). In the second place, an infection acquired in hospital may make little obvious change in already sick patients, though it may prolong the period of illness,

or eventually kill the patient. An obvious illustration is again found in wounds; the addition of *Strept. pyogenes*, to a wound already septic as the result of infection with *Staph. aureus*, may not be at first clinically apparent, but the subsequent history of the wound is that of a severe streptococcal infection (Miles, Schwabacher, Cunliffe, Ross, Spooner, Pilcher & Wright, 1940; Spooner, 1941). Again, children convalescent from infection by one type of diphtheria bacillus, may be re-infected by diphtheria bacilli of another type (Glass & Wright, 1938; Wright, Shoné & Tucker, 1941). In the third place, the patient's response to added infection may not take the form of a gross, acute disease. He may become a healthy carrier of the infecting organism, or he may suffer from an infection which is clinically silent. In a children's ward observed for one year, Wright (1940) found that of all the children who acquired a *Strept. pyogenes* in the throat, only 25% showed any signs of infection. The healthy carrier, by definition, does not suffer from the infection, but he becomes a reservoir of the organisms and a menace to other patients who may be highly susceptible to the infection. To the susceptible patient, the carrier and the silently-infected patient are in fact a greater menace than the manifestly-infected patient, for they display no danger signs whereby their condition may be recognized, and the risks of transfer guarded against.

Silent infections and the healthy carrier-state are indistinguishable by a single clinical or bacteriological examination but, in some cases at any rate, it is clear that some of those who carry pathogens without suffering from manifest disease, do in fact suffer disabilities from the presence of the organism in the body. For instance, in one survey (Gissane, Miles & Williams, 1944) the average period of treatment for minor lacerations of the hand treated by excision and suture was

Clinically and bacteriologically clean wounds	15.6 days
Clinically clean, but "infected" wounds	18.2 days
Septic wounds	25.4 days

Here the average healing time of the silently infected wounds is 20% higher than that for clean wounds, a sufficiently striking figure for small wounds; the healing time is increased 60% in the septic wounds. For larger wounds, there are few precise records of the effect of added infection, though there is general agreement that infection *per se* delays healing. In one series of air-raid wounds of the head, the average healing time of those with added streptococcal and staphylococcal infection was over 100 days; those without added infection healed in an average of 35 days (McKissock *et al.*, 1941).

It follows from these preliminary remarks (a) that preventive measures must cover more than obvious existing risks; to meet greater possible risks they must be made as infection-proof as is practicable; (b) that preventive measures must

aim at reducing the spread of mild as well as severe infection, and at preventing the increase of the carrier-state and of silent infections; and finally (c) that the criteria of an added infection are in the last analysis bacteriological, not clinical.

The crippling or fatal added infection, however rare its occurrence, is an index of gaps in the hospital's defence against infection, gaps through which, it would be salutary to assume, mild and silent infections are all the time creeping. There is no good reason why a patient or a member of the medical staff should suffer, even mildly, from an avoidable infection acquired from other patients or members of the hospital staff. To allow him to do so is both inhumane and uneconomical. In times of war, when the demand on manpower and medical services becomes acute, avoidable infection is even less defensible.

Sources of Added Infection

The three main types of added infections are, in order of their importance and prevalence: respiratory; gastro-intestinal; and infections of skin, external mucous membranes and wounds. With the exception of wounds and burns—infections which attain a peculiar predominance in war-time—these infections bear most heavily on the child population (*Medical Research Council*, 1944). From the hospital point of view, the reservoirs of all these infections are excreta and discharges (including droplets from the upper respiratory tract) from manifest cases of the various diseases, or from healthy carriers. From the upper respiratory tract come bacteria, such as *Strept. pyogenes*, *Staph. aureus*, pneumococci and meningococci, the bacilli of diphtheria, whooping-cough and tuberculosis; and viruses, or presumed viruses, like the agents of measles, chicken-pox, rubella, mumps, infectious hepatitis. From faeces, vomit and urine may come *Salmonella* and dysentery bacilli, protozoa like *Giardia*, and perhaps the causal agent of the so-called non-specific enteritis. And from infected skin, conjunctivae, mouths, external genital tracts, and from infected wounds may come discharges bearing bacteria of the numerous pathogenic species, both aerobic and anaerobic, known to infect these places.

Preventive Measures: Some Important Considerations

It is obviously impossible to eliminate these reservoirs of infection from among the patients whose infection may have brought them to hospital. Elimination of carriers from the hospital staff is both possible and desirable, but in some cases it is impracticable. It may be impracticable if the carrier-state is so common that to dismiss the carriers would necessitate closing the hospital. The nasal carrier-rate of potentially pathogenic *Staph. aureus* in a nursing staff may be as high as 80% (Miles, Williams & Clayton-Cooper, 1944). No maternity home, for example, faced with an outbreak of staphylococcal "pemphigus" among the infants, could afford to send 80% of its nurses off duty. The same consideration might apply to carriers of the meningococcus. In other cases, as with *Salmonella* bacilli, the probability of added infection is too great, and the consequences of infection are too serious, to allow a carrier to continue in hospital service.

It is outside the purpose of this article to discuss the cure of intestinal or respiratory carriers. In any event, evidence of the complete cure of a carrier state, especially in the upper respiratory tract, is hard to obtain, as absence of the organism in question from the samples examined bacteriologically may indicate only a temporary absence of the organism from the superficies of the mucous membrane. And it is known, for example, that *Strept. pyogenes* (Straker, Hill & Lovell, 1939) and pneumococci (Smillie, Calderone & Onslow, 1943) may reappear in the throat after a prolonged naturally-occurring absence. Nevertheless, measures which apparently cure or diminish a carrier-state have their use, as at least they reduce the load of bacteria which the carrier disseminates through his surroundings. Of simpler measures which appear to achieve this end in the upper respiratory tract, we may cite the successful use of penicillin (Delafield, Straker & Topley, 1941) and sulphathiazole snuffs (Delafield & Straker, 1941; Thomas, 1941; Goldman & Patterson, 1942) for the treatment of nasal carriers of *Staph. aureus*, *Strept. pyogenes* and *C. diphtheriae*, the treatment of throat carriers of *C. diphtheriae* by aerosols of sulphapyridine (Legros, 1943) and of throat carriers of *Strept. pyogenes* by tonsillectomy and sulphanilamide treatment (Chesterman & Scandrett, 1940).

Since only a limited attack can be made on the reservoirs of infection, preventive measures are usually devised closing the channels of infection. It is customary to distinguish spread of infection by (a) contact, which may be direct (immediate) or indirect (mediate)—such as transmission by hands, instruments, utensils, clothes, food, flies, etc.; (b) by droplets; and (c) by the air.

It is certain that a number of infective agents, among them bacteria and viruses, can remain infective for long periods as dry or semi-dry particles, small enough to be carried considerable distances by relatively feeble currents of air. These particles may be formed by the disintegration of dried infective discharges and excretion. Explosive respiratory discharges, such as accompany sneezing, coughing and talking, are particularly prolific in the production of the particles. Fluid droplets of various sizes are discharged in these explosions. Wells (1934) distinguished the relatively large liquid droplet from the small particles, which in the course of a few seconds dry up and form a readily air-borne "droplet nucleus". It is the infected droplet nuclei that infest the air. The importance of the distinction has recently been emphasized by Hare (1940), who showed by bacteriological methods that the larger droplet depends upon the explosive impulse for its dissemination, and has a horizontal range of about 1 metre only. The maximum horizontal range, determined by flash-photography of droplets during expulsion, is about 2 metres (Bourdillon & Lidwell, 1942). The droplet is not, in fact, truly airborne (Mackie, 1942) and may logically be considered as an example of mediate contact infection. There are, however, many other sources of airborne infective particles besides the droplet-nucleus. The large droplet that falls to the ground or on to bedclothes, and infective discharges that contaminate dressing, clothes and bedding, disintegrate and eventually add their quota of infective dust to the air. The prevalence and dangers of dust-borne *Strept. pyogenes* (Cruickshank, 1935; Allison & Brown, 1937; White, 1937; Cruickshank & Godber, 1939; Cruickshank & Muir, 1940; Kelsey, 1941; Willits & Hare, 1941; Edward, 1944) and *C. diphtheriae* (Crosbie & Wright, 1941) are well established.

There are then two modes of transmission, air-borne and contact. The relative importance of the two modes of spread depends firstly on the survival of different infective agents in the dry particles of dust, and secondly on the mode of infection in each disease. It appears (Mackie, 1942) that staphylococci, haemolytic streptococci, pneumococci, the diphtheria bacillus, bacterial spores, and tubercle bacilli survive for relatively long periods in the dry state. *Haemophilus*, the plague bacillus, *Salmonella* and dysentery bacilli, and the cholera vibrio die rapidly. Among the viruses, those of variola, vaccinia, psittacosis and poliomyelitis appear to survive well; the influenza virus (Edward, 1941) is moderately resistant. With regard to the mode of infection, air-borne infections are paramount in respiratory disease, as even a dilute infestation of the air will tend with continuous breathing to concentrate in the upper respiratory tract of the patients at risk, and the opportunity for the aerial dissemination of infective agents from those already infected is obviously great. Air-borne infections probably occur to some extent in wounds (Miles *et al.*, 1940). In the recorded outbreaks of added infection of wounds, however, the observed opportunities for contact infection have been so great that the rôle of air-borne bacteria cannot be judged with any accuracy. It may nevertheless be assumed to have been small, because infective particles fall slowly from the air on to the exposed wound; though big wounds and extensive burns, the large area of which entails long periods of exposure during dressing, must be considered as relatively susceptible to air-borne infection.

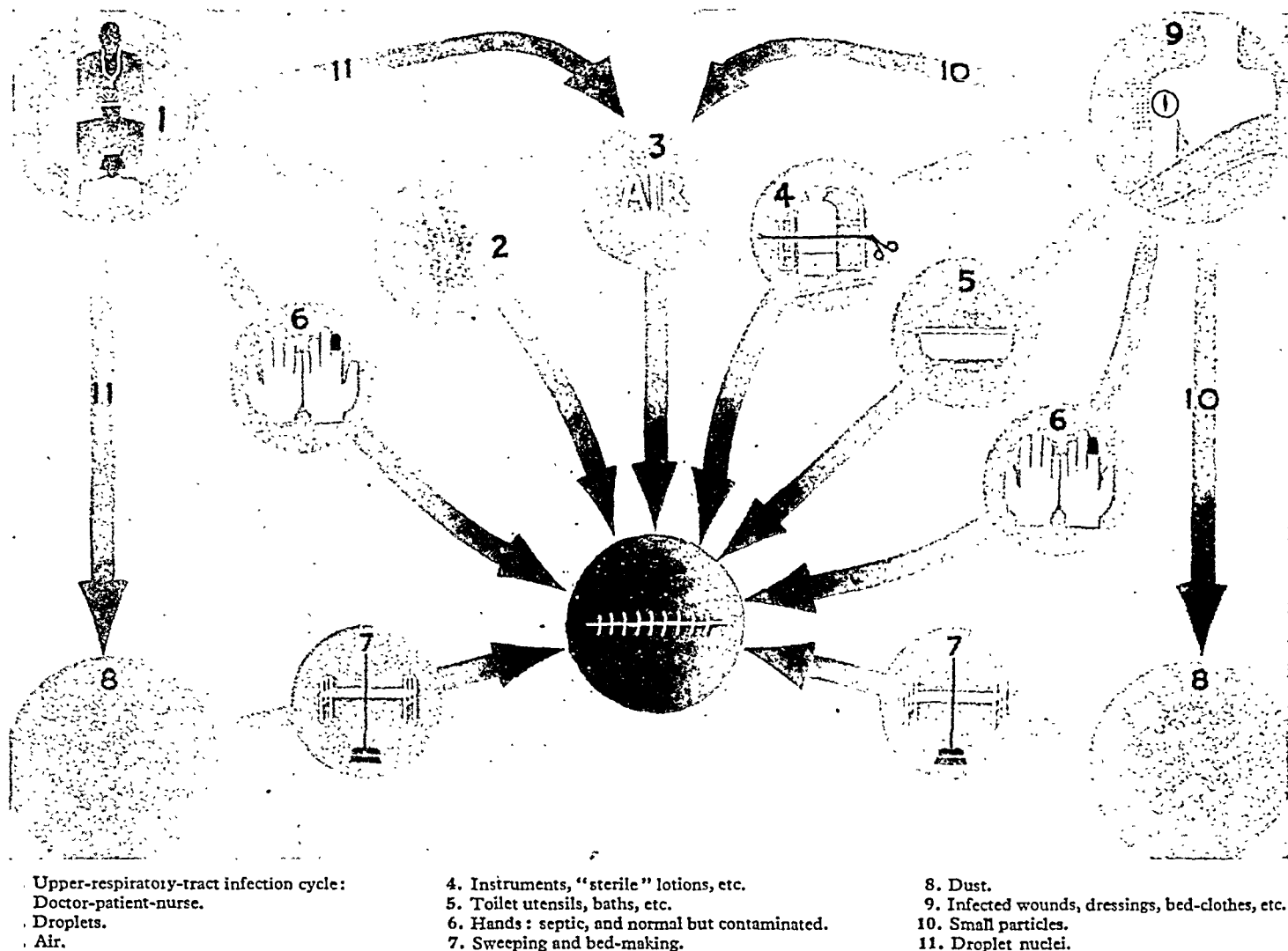
There appears to be little opportunity for the rapid drying of infective intestinal discharges, and their subsequent disintegration into air-borne particles. Feeding utensils and food are of prime importance in the spread of intestinal diseases. Other vehicles are important as they are related to the ingestion of infective material, to excretion on the part of the patient, and to the handling and disposal of excreta by the hospital staff.

The possible vehicles of skin and wound infection are, like those of intestinal infections, too numerous for detailed mention. Even a perfunctory survey of an operating-theatre, out-patient or ward routine will reveal an abundance of opportunity for the transmission of infective material.

if it is assumed that infective material can be introduced almost at any point in the routine. As we have seen, the silently infected patient is a danger because his potentialities are unrecognized; in the same way, the silently contaminated hand, utensil or instrument is equally dangerous. To take an example, in a ward containing one or two wounds infected with *Strept. pyogenes*, the coccus may be grown, not only from the wound and the obviously soiled inner dressings of

sampler (Bourdillon, Lidwell & Thomas, 1941) as well as other devices for efficient sampling of the bacterial content of the air, have permitted tests of various methods of diminishing or killing air contaminants. Some of these methods, like the installation of air-conditioning plants capable of removing bacterial particles, are prohibitively expensive for most hospitals, and in war-time the necessary apparatus may be unobtainable. In this category, also, comes the use

HOW A CLEAN WOUND MAY BECOME INFECTED



the infected patient, but also from the apparently clean outer dressing, the bandage, the patient's skin for distances up to 10 cm. from the wound, his pyjamas, pillow-cases, sheets, blankets, bed-rail; from the dust under his bed, the curtains of his screens placed round the bed, from the grease-line of wash-bowls and baths (often in communal use in the ward) that he uses. It will be obvious that a nurse who has nothing to do with the actual dressing of that wound may carry the streptococcus to other patients merely by touching the outer bandage, adjusting the bedclothes or moving the bed.

Available Modes of Closing Channels of Infection

Air-borne infection: Air-borne infection must depend for its success on a relatively high concentration of the infective particles in the environment of the susceptible person, and for this reason it is likely that a great many of its dangers can be guarded against by dilution of the infective agent. It is well recognized that the bacteria of air and dust are sterilized in sunlight, but less well recognised that diffuse daylight is bactericidal (Soloway, Solotorovsky & Buchbinder, 1942) even after passage through media which, like ordinary window glass, are impervious to ultra-violet rays (Garrod, 1944). Ventilation, intelligently applied, has been and will remain a simple bulwark against air-borne infection. There are, however, many situations for which the remedy of ventilation is inadequate or inapplicable, and in recent years many attempts have been made, either to sterilize contaminated air, or to shield the patient from it. Indeed, spectacular advances in the control of added infection have been made particularly in the realm of air-borne infection. The Wells air centrifuge (Wells, 1933) and the Bourdillon slit-

of batteries of ultra-violet lamps for air sterilization, though there is good evidence that ultra-violet irradiation is lethal to aerial suspensions, for example, of viruses (Edward, Lush & Bourdillon, 1943) and that the incidence of various respiratory infections of children in wards and schoolrooms—measles (Wells, Wells & Wilder, 1942), varicella (Green, Barenberg & Greenberg, 1941) and general upper respiratory infections (Barenberg, Greene & Greenspan, 1940; del Mundo & McKhann, 1941; Robertson, Doyle & Tisdall, 1943)—is markedly reduced by irradiation of the air in wards and schoolrooms. On the other hand, Sommer and Stokes (1942) report no detectable effect of irradiation on the incidence of pneumococcal infection in children's wards, though both irradiation and glycol vapours reduced the infection rate in mice that had been exposed in wards contaminated with droplet-nuclei containing influenza virus or streptococci (Henle, Sommer & Stokes, 1942). Glycol vapours in concentrations tolerable by the human being are lethal to artificial suspensions of bacteria (Puck, Robertson & Lemon, 1943) and influenza virus (Robertson, Loosli, Puck, Bigg & Miller, 1941), and their use in a children's ward (Harris & Stokes, 1943) was accompanied by a marked reduction in the incidence of tracheobronchitis and the common cold, as compared with a control ward. Hypochlorite sprays are effective against suspended viruses and bacteria (Baker, Finn & Twort, 1940; Challinor, 1943; Edward & Lidwell, 1943) and have been used with apparent success in suppressing epidemics of respiratory infection in military camps (Middleton & Gilliland, 1941). Pulvertaft (1944) emphasizes the simplicity of their application—by atomization of hypochlorite solutions in household insecticide-spraying pumps. Lovelock, Lidwell & Raymond (1944) have recently demonstrated

that lactic acid sprays have a marked bactericidal effect on artificially- and naturally-infected air. The different lethal agents vary in the range of conditions over which they are effective, but to some extent all of them are less effective in dry atmospheres, and in air containing high proportions of inert dust-particles.

There are even simpler methods of reducing the contamination of the air. Bacteria-containing dust sediments with comparative rapidity. For instance, though the bacterial content of ward air rises considerably at bed-making and sweeping, it usually drops to a low level in half to one hour after activity in the ward is reduced to a minimum. Advantage may be taken of this sedimentation-rate by the application of oils to the floor and other smooth surfaces of the ward, and to bed-linen, blankets and curtains. The oil not only prevents the dissemination of bacterial dust during ward activities like sweeping and bed-making, but also (Thomas, 1941) holds newly-formed bacterial dust as it settles after its discharge from the carrier or the infective patient (van den Ende, Lush & Edward, 1940; van den Ende, Edward & Lush, 1941; van den Ende & Spooner, 1941; van den Ende & Thomas, 1941). Paraffin or commercial white oil is used. The method is suitable for wooden and linoleum floors, and both cotton and woollen bed-clothing and garments can, by a simple and cheap laundry technique (Harwood, Powney & Edwards, 1944), be impregnated with bacteria-holding concentrations of oil. Material so treated is highly effective in holding bacterial particles. By these means, Wright, Cruickshank & Gunn (1944) have recently produced a marked reduction in the incidence of streptococcal added infection in one measles ward, as compared with that in a similar "oiled" control ward. Anderson, Buchanan & MacPartland (1944) for 4 winter months observed respiratory infections in two military units which differed only in that the floors of all the huts in one of them were oiled at monthly intervals. The average weekly rate of acute respiratory infection per 1,000 men was 7 in the "oiled" unit, and 38 in the control.

Contact-infection: There are no spectacularly successful, or simply applied techniques for the reduction of contact-infections. The channels of contact-infections are many and various, and each may require a separate mode of closing. It is probable that great improvements would follow the abolition of large open wards and the division of hospitals into a number of single-bedded units and small wards (Medical Research Council, 1944). But no subdivision of this kind will be effective unless all possible contact-transmissions are prevented. To take an obvious example, the most elaborate design of ward will fail to check the spread of contact-infections in a children's ward if the duties of one nurse include routine attendance on the patient's excretions, and preparation of his food. The principles which govern the design of precautionary methods are usually simple; the chief difficulty in applying them is failure to recognize where the risks of infection are greatest, and it is here, at any rate with infective agents that are readily cultivable, that a bacteriological survey is chiefly valuable. The main reason for the failure of precautions is failure to work intelligently from the principles. For instance, the ritual observance of a rule that every nurse should wash her hands after a visit to the water-closet will have little effect on added infection of the nursing staff by Sonne's dysentery bacilli if the wash-basin is outside the water-closet, for the door handle in each case is thoroughly contaminated before the hands are washed.

As an illustration of the complexity of the problem, we may consider the elimination of hospital infections of clean wounds in a surgical ward. Our primary aim is to protect the wound from potentially pathogenic bacteria; we cannot hope to eliminate all bacteria from the ward environment at the time of dressing.

With few exceptions (e.g. the brain), freshly cut tissues of the body appear to be bactericidal enough to kill small numbers of saprophytic organisms, without the mediation of detectable inflammatory reaction. The uneventful healing of large numbers of operation-wounds, made in theatres that are certainly not bacteria-free, is sufficient evidence of this point, though the possibility of harmful "silent" infection cannot be excluded in operation-wounds that heal by "first intention." Bearing in mind the "silent" infections, Gudin (1942) pleads strongly for the elimination of all possible sources of infection, and insists that a true sterile healing of wounds cannot be

guaranteed unless the operation is performed in a special theatre whose walls, furniture and instruments are sterile, by persons completely covered to contain their personal bacteria, upon a patient whose skin is completely sterile. Gudin's "integral asepsis" is devised for theatre work; and though his analysis of the dangers of theatre contamination may be read with profit by those designing aseptic methods for the ward, the method is not strictly applicable to wards, where the problem is one of local bacteriological control of a small area of operation.

We have for the most part to guard against *Staph. aureus* and *Strept. pyogenes* which, together with the faecal coliform bacilli, are the chief cause of hospital infection of wounds (Miles *et al.*, 1940; Williams, Clayton-Cooper, Howat & Miles, 1945). The figure [see page 278] illustrates the situation of a clean wound exposed for dressing in such a ward. There are two main reservoirs of these organisms, namely, already infected wounds, and the upper respiratory tract of patients and personnel. The carriage of *Strept. pyogenes* in the throats of 5-15% of normal persons is well recognized. It is less well recognized that *Staph. aureus* is carried, usually in profusion, in the nasal cavity of about 50% of normal adults, and that the carriage is more or less persistent (Miles, Williams & Clayton-Cooper, 1944). The dangers of infected droplets, droplet-nuclei, from these sources have already been discussed. The other reservoir, the infected wound, is a profuse source of the two cocci. It cannot be too strongly emphasized that not only are the wound exudate, and the inner dressings of such wounds, full of organisms, but also that the skin for a large area around the wound, the skin of the patient's hands, and all the bed-clothes, may be holding the infected dust. Some of the places where *Strept. pyogenes* may lie in such a ward have been listed above. *Staph. aureus* will also be found in these places. And we may add the personal bandage-scissors of the nurses; the aprons, coats and gowns of the staff, the hands of staff; instruments, lotions, and gauze or lint contaminated in bulk when samples are taken with soiled instruments or hands during the course of a dressing. The two cocci may spread by means of instruments and hands of medical staff. They may spread via wash-bowls and baths, where they collect in the grease-line, and defy all but the most rigorous antiseptic treatment.

Bacteriologically Acceptable Dressing-Techniques

There are two alternatives for the safe dressing of wounds. Either the wound may be dressed in a theatre or side-room, the whole of which is under full control, or the dressing may be done in a ward, where an attempt is made to create local conditions of asepsis round the exposed wound. The dressing theatre has many advantages, and it may prove to be a necessity in the treatment of burns, which are peculiarly susceptible to added infection. Nevertheless, it is often convenient to dress wounds in a general ward, and it should be possible to do so in comparative safety from infection.

Some of the precautions necessary to achieve local control of infection in the surgical ward are obvious. Droplet-infection is prevented by rigorous masking, using masks with at least one layer of an impermeable material like cellophane. Soiled dressing-materials—plasters, bandages, etc., must be removed and disposed of with the minimum of disturbance into deep, capacious discard-bins. Plasters, which may be impregnated with dried bacteria, should be damped before removal. The wound must be exposed as little as possible, and dressed by a no-touch technique¹ (as distinct from the "dripping-finger" method of manipulating the wound with scrubbed wet hands). The essentials of the no-touch technique are as follows. Dry sterile forceps must be used for all manipulations of the wound. The hands of the dresser need not be surgically sterile, but must be clean and dry. All material for the dressing of the wound is passed in forceps to the dresser by a person whose sole duty is to look after a trolley containing all clean and sterile material. A third person should be available to help by adjusting clothes, bandaging, and sterilizing instruments, etc., for use. This third person, like the dresser, must wash carefully between each dressing, or he may become a dangerous vehicle of infection, as from each infected patient he may be liberally contaminated by touching bed-clothes, pyjamas, healthy skin, and all the outer dressings. Persons

¹ [The no-touch technique of dressing wounds has been described in detail by the Medical Research Council (1941).]

with infections of the hand must not be allowed to dress the wound; and all persons who handle the wound, in any capacity, must be thoroughly familiar with the elements of prophylaxis against contact infection (*Medical Research Council*, 1941).

The more thorough methods of eliminating dust have been discussed above. Apart from these, much can be done by damp-dusting and -sweeping, and the cessation of all dust-raising activities in the ward half-an-hour before, and throughout, the period when wounds are dressed. It is most important that the precautions should be observed by *all* hospital staff concerned. Often, when the most rigorous precautions are taken to prevent the dresser of the wound from spreading infection, great latitude in this respect will be allowed to the visiting surgeon, the porters, to x-ray attendants, masseurs and ward-maids.

Simple revisions on these lines have proved successful in reducing added infection of wounds. McKissock *et al.* (1941) reduced a gross streptococcal infection-rate of 31 % to 2 % in an air-raid casualty ward. In a septic ward treating industrial accidents, where the reservoirs of infection were numerous, the incidence, per wound-weeks at risk, of *Strept. pyogenes* infection was 14 %, and of *Staph. aureus* infections, 100 %. After a revision of ward technique, these figures fell to 18 % and less than 1 %, respectively (Williams *et al.*, 1945). Ascroft (1944) has also made striking reductions in "clean" wound infection by simple revision of certain nursing procedures. Revision need not mean elaboration and a consequent increase in work for the hospital staff, for many existing precautions are often redundant, and their elimination allows ample time for taking more rewarding precautions. Revised dressing methods, in fact, once they are learned, are quicker in performance than some of the older methods (Gissane *et al.*, 1944).

Direct Protection of the Patient against Added Infection

We have so far discussed elimination of the reservoirs of infection, and stoppage of the channels of infection. There remains a third method, namely, the enhancement of the patient's powers of resistance either by specific immunization against prevalent hospital infections, such as diphtheria and pertussis, or by the administration of prophylactic doses of chemotherapeutic agents. Both are beyond the scope of this article, but mention of the second raises a point of some

importance in wound infection. It is believed by some that the success of the sulphonamides and penicillin against the Gram-positive organisms to some extent excuses a perfunctory method of aseptic handling of wounds. The view is quite unjustified, for some strains of the pyogenic organisms are, or may become, drug-fast; moreover, as the extensive survey of Meleney and his colleagues suggests (Meleney, 1943), the prophylactic use of sulphonamides may have little effect on the incidence of added or late-developing infections; and finally, the organisms that are relatively insensitive to these agents—the coliform bacteria, *Ps. pyocyanea*, *Proteus vulgaris*, *H. para-influenzae*, etc.—are by no means negligible as causes of severe infection, and of severe residual disabilities in the ultimately healed wound.

Conclusion

In conclusion, it should be emphasized that the difficulties of preventing added infections come more from the psychological obstacles to easy reform, than from the technical problems of prophylaxis. It is essential that the staff of hospitals should be educated to recognize the reservoirs of infection, their magnitude and dangers, and to meet the dangers by methods that are flexible enough to change when new risks of added infection are discovered. Rules of procedure must be intelligible as applied principles; they must not be mere lists of commands; if they are, they will fail because they will be obeyed blindly when changing circumstances dictate their modification.

A great deal can be achieved without elaborate apparatus, and without specially-trained staff. Elaborate measures like ultra-violet irradiation, or the use of dressing theatres, may be necessary. Such measures are often credited with a success to which they are not fully entitled; for consciousness, on the part of the staff, of the infection risks that the elaborate measures have been designed to meet, may lead to a general improvement in the performance of the simpler precautionary duties.

In the future, precautions will be more easily taken if hospitals are designed for preventive as well as for administrative convenience. But no elaboration of design will be effective unless the education of the doctor and the nurse inculcates not rules for prevention, but the general principles from which the *ad hoc* methods of attack can be readily devised.

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555

THE CHEMICAL NATURE OF BACTERIAL ANTIGENS

W. T. J. MORGAN, Ph.D., D.Sc.

Lister Institute of Preventive Medicine

Our present knowledge of the chemical nature of the somatic antigens of bacteria originated in the first place from the results obtained by applying immunological techniques, which were elaborated during the early part of the present century, for distinguishing between the antigenic components of various species of bacteria. The isolation and identification of these antigenic complexes was undertaken as soon as their qualitative detection and quantitative measurement had been established by these techniques.

Pick (1912) observed that typhoid cultures that had been rendered protein-free by treating them with trypsin and pepsin, and by subsequent boiling to remove soluble protein, contained a substance which formed a precipitate in the presence of typhoid immune-serum. Similar observations were recorded by Dochez & Avery (1917) for *Pneumococcus*, and by Zinsser (1921) who worked with *Pneumococcus*, *Staphylococcus* and the typhoid bacillus. Somewhat later, serologically-active substances were isolated by chemical procedures from each of the main types of *Pneumococcus*, and were identified as complex polysaccharides which are located in the bacterial capsules of the different strains (Heidelberger & Avery, 1923, 1924; Avery & Goebel, 1933; Heidelberger, Kendall & Scherp, 1936; Brown, 1939; Brown & Robinson, 1943). The methods used in the investigations have been extended to many pathogenic and non-pathogenic strains of bacteria in the Gram-positive and Gram-negative groups.

In almost every instance the purified specific-soluble substance was found to lack significant antigenic properties, as it failed to induce the formation of a type-specific precipitin, agglutinin or protective antibody in the serum of rabbits that had received intravenous injections of polysaccharide material. As a result of this work, a conception of antigenicity which attributed the specific immunological properties of a complete bacterial somatic antigen to a polysaccharide constituent, and the antigenic properties of the complete bacterial complex to a combination of this important constituent with some other chemical component, came to be generally accepted and led to the idea that the difference between a virulent and an avirulent strain of the same organism is the presence in the former of the specific antigenic complex, which is not found in the avirulent form. Substances, such as the specific polysaccharides, that do not possess complete antigenic power but have the capacity of reacting *in vitro* with the immune-sera prepared by using the whole antigen, have been termed haptens by Landsteiner.

In the space available here it is not possible to deal in detail with the chemical nature of the large number of specific bacterial somatic substances that have been described. The account that follows is, therefore, limited to a description of one or two examples of typical haptens and antigens selected from the groups of Gram-positive and Gram-negative organisms. The chemical nature of the so-called bacterial toxins and the antigenic complexes of animal and plant viruses are not discussed.

Specific Components of the Antigenic Complexes of Gram-positive Bacteria

The polysaccharide components of the type-specific antigens of the pneumococci were among the first bacterial haptens to be isolated and identified, and, of these biologically

important complex molecules, our knowledge of the specific polysaccharide of *Pneumococcus* Type III is more complete than that of any other bacterial polysaccharide. The polysaccharide of *Pneumococcus* Type III is broken down by acid hydrolysis into aldobionic-acid units, each composed of one molecule of glucose and one molecule of glucuronic acid, united by a glycoside link involving the reducing (aldehyde) group of the glucuronic acid and carbon atom 4 of the glucose molecule. The aldobionic acid molecules are likewise joined together by a glycoside link which involves the reducing group of the glucose component and the hydroxyl group attached to the third carbon atom in the glucuronic acid molecule. According to Reeves & Goebel (1941) the polysaccharide molecule may be formulated as

-4 glucose-1 : 3 glucuronic acid-1 : 4 glucose-

During work on the serological differentiation of the pneumococcal types, it had been observed that there was a considerable degree of overlapping in the specific reactions of Types III and VIII of the pneumococcus. With the isolation and subsequent examination of the specific polysaccharide from the Type VIII organisms by Goebel (1935), it became evident that the specific polysaccharide of each of these types contains a common aldobionic acid component, and thus it would appear that it is this component which is responsible for their overlapping specificity. Determination of the proportions of the constituent molecules in each of the two polysaccharides revealed that the Type VIII polysaccharide contained glucose units approximating to the ratio of 7 molecules of glucose to 2 of glucuronic acid, as compared with a 1 : 1 ratio for the Type III polysaccharide.

Avery & Goebel (1933) showed that the component responsible for the type-specific reactions of *Pneumococcus* Type I is an acetylpolysaccharide which possesses acidic characters, contains 6.0% of acetyl groups and 4.8% N, about a third of which is probably present as a primary amino group. The substance is strongly dextro-rotatory, $[\alpha]_D + 255^\circ$, and gives rise to 32% of reducing sugar on acid hydrolysis. This polysaccharide was found to possess the unusual property of inducing the formation of protective antibody. Thus mice, when injected intraperitoneally with minute quantities of the acetylpolysaccharide, responded with an active immunity to subsequent infection with the homologous organism. On the other hand, no type-specific precipitins, agglutinins or protective antibodies were demonstrable in the serum of rabbits that had received repeated intravenous injections of the Type I acetylpolysaccharide. These experiments revealed, therefore, points of difference between the antigenic properties of the acetylated polysaccharide and those of the type-specific antigen of the intact virulent coccus, and indicated that the native type-specific antigen had not been isolated. The acetylated polysaccharide is clearly an important component of the type-specific antigenic complex, but it does not possess the full antigenicity of the naturally-occurring antigen.

The kind of substance with which the specific polysaccharides in the different types of pneumococci are combined to render them fully antigenic and thus able to induce the formation of the homologous type-specific immune-sera, is not known with certainty. If, as appears probable, the proteins that are present in all types of pneumococci are similar, then, in the light of some recent observations with

other antigenic complexes (see Morgan & Partridge, 1941; Morgan, 1943a; 1943b), it may be anticipated that the specific polysaccharide-protein combination will prove to be antigenic and will give rise to an immune-body that is specific for the polysaccharide component of the complex, and thus specific for the pneumococcal type from which the polysaccharide had been isolated. But it is doubtful whether, up to the present time, there is any record of the isolation and identification of a complete type-specific somatic antigen that is associated with a capsular polysaccharide of a Gram-positive organism.

The antigenic analysis of haemolytic streptococci has revealed a different type of antigenic complex, for the type-specific properties reside in a protein substance, M, and in another unidentified type-specific compound T (Lancefield, 1940; Zittle, 1942). The M protein can be isolated from the virulent organism by extraction with 0.05 N HCl and purified by salt fractionation, iso-electric precipitation, and dialysis. The species-specific properties of most of the strains of human origin (Group A) are due to a polysaccharide which contains 1.7% N, yields 87% of reducing substances after acid hydrolysis and possesses a strong *laevo* rotation (Zittle & Harris, 1941). The capsular substance of the haemolytic streptococci consists largely of hyaluronic acid, a polysaccharide built up from molecules of glucuronic acid and N-acetylglucosamine (Kendall, Heidelberger & Dawson, 1937). The capsular material in this instance appears to play no part in the specific serological reactions of the haemolytic streptococci and cannot therefore be considered to be the specific haptin in spite of its location in the bacterial capsule. It seems, however, to be a factor of definite significance in the virulence or invasiveness of these organisms (Seastone, 1943).

The specific capsular substance of virulent strains of the anthrax bacillus is not composed of a polysaccharide, as for most organisms, but consists of a protein-like substance which is composed of d(-) glutamic acid molecules linked together to form a long-chain polypeptide (Ivánovics & Bruchner, 1937; Ivánovics, 1940). The substance gives precipitation with the sera of rabbits hyper-immunized with killed encapsulated anthrax bacilli; and such sera can protect mice against anthrax infection. The capsular material is built up from the "unnatural" form of glutamic acid, and the suggestion has been made that the resistance of this substance to the action of the tissue-enzymes is most probably responsible for the virulence of the encapsulated form of the organism. The somatic substance of both the virulent and avirulent bacillus contains an antigen, the specificity of which is determined by a nitrogenous polysaccharide, composed of *d*-galactose and *d*-glucosamine.

Type-specific polysaccharides have been obtained from *Staphylococcus*, Types A and B, by Wieghard & Julianelle (1935), but the corresponding antigenic complex has not been isolated. The more recent work of Verwey (1940) suggests that there is also present a type-specific antigenic protein. This material reacts in high dilution with homologous immune-sera prepared by injecting animals with whole organisms or with the protein substance itself.

Isolation of Specific Somatic Antigens from Gram-negative Bacteria

The chemical nature of the somatic antigens of the Gram-negative bacteria has in some instances been investigated in considerable detail. Indeed, careful study of the antigens of the dysentery-typhoid group of organisms has revealed much of the inner structure of these complex molecules and has shown that in many biologically unrelated organisms the general make-up of the characteristic somatic antigen is very similar.

Until about 10 years ago attempts to separate the somatic antigens from bacteria were unsuccessful, but in 1933 Boivin and Mesrobianu devised a simple technique whereby antigenic material could be obtained from Gram-negative organisms by extracting the wet bacteria with dilute trichloroacetic acid (pH 1.0-2.0) at 0° C. The antigenic complex passed into solution and was freed from bacterial bodies by centrifugation and filtration. About the same time, and quite independently, Raistrick & Topley (1934) found that by the action of trypsin on *Bact. aertrycke* it was possible to bring the specific somatic antigenic complex into solution. The digestion was carried out at pH 8.3-8.5 for several days at 37° C. Freeman, Challinor & Wilson (1940), using

the same method of isolation, extended these observations, compared the properties of antigenic material isolated from organisms that had been grown on ordinary and synthetic media, and concluded that the essential antigenic complex could be obtained in a state approaching chemical homogeneity from cultures grown on either medium.

A method for the isolation of bacterial antigens from Gram-negative organisms which avoids the use of an acid or alkaline medium, and which can be carried out at a low temperature, was introduced by Morgan (1937) in order to minimize the risk of inducing changes in the antigenic complex during the process of isolation. The extraction process was based on the solubility of the antigenic material in water-soluble organic solvents, anhydrous diethyleneglycol being the one most extensively used. The use of a solvent of this kind allows the antigen to be separated from 90-95% of the total material of the bacterial bodies and thus renders its subsequent isolation from the non-specific somatic substances relatively easy. Furthermore, the use of anhydrous organic solvents reduces the possibility of extracting enzymes from the bacterial bodies that are destructive to the antigen by subsequently attacking the antigenic complex when, at a later stage in its purification, it is obtained in aqueous solution.

Chemical Nature of the Somatic Antigens of Gram-negative Organisms

The first insight into the nature of the specific somatic antigens of Gram-negative bacteria was obtained by Boivin & Mesrobianu (1933), who showed that the material extracted by trichloroacetic acid from certain strains of *Salmonella* could be split by gentle acid hydrolysis into a polysaccharide that was specific for each specimen examined, and a fatty or phospholipin component which possessed no obvious immunological property. In a long series of papers, Boivin and his co-workers (see Boivin & Mesrobianu, 1935; Mesrobianu, 1936; Soru & Combesco, 1940) showed that the polysaccharide-phospholipin type of antigenic complex was present in many different species of Gram-negative bacilli. The complexes were found to be toxic for animals and were believed to be free from protein. Raistrick & Topley (1934) considered that, from the evidence then available, a final conclusion as to the composition of the antigenic complex could not be reached, other than that it contained the specific polysaccharide in an antigenic form. Topley, Raistrick, Wilson, Stacey, Challinor & Clark (1937) subsequently concluded that the antigenic material isolated by means of tryptic digestion of *Bact. aertrycke* and *Bact. typhosum* was similar to that isolated by Boivin by means of trichloroacetic acid. These workers examined antigenic extracts that contained more than one type of antigen, and showed that certain qualitative tests, such as the formation of a precipitate with aluminium sulphate or uranium acetate, could indicate the presence of the "virulence" or "Vi" antigen (Felix & Pitt, 1934) in material isolated from strains of *Bact. typhosum* which contained this antigen in addition to the characteristic O-somatic antigen. They also pointed out that the O-antigen in the presence of Vi-antigen was much more resistant to hydrolysis by 0.1 N acetic acid at 100° C. than the O-antigen alone.

Morgan (1937), Henderson & Morgan (1938) and Morgan & Partridge (1939, 1940, 1942) considered that the O-somatic material extracted by diethyleneglycol from *Bact. dysenteriae* (Shiga) and *Bact. typhosum* was a homogeneous molecular complex containing a polypeptide-like or protein component, a specific polysaccharide and a phospholipin complex. The degradation of these antigenic complexes by means of anhydrous formamide was studied in considerable detail and it was shown for the antigen of *Bact. dysenteriae* (Shiga) that the phospholipin ($[\alpha]_{5461} + 12^\circ$; N, 1.8%; P, 3.9), although more or less firmly bound to the other components, could be removed by means of the dissociating action of formamide without inducing a significant change in the immunological properties of the antigen. Thus the phospholipin-free material was found to be fully antigenic, and induced in rabbits the production of specific agglutinins and precipitins and the "Shiga" heterophile immune-body. It appears, therefore, that the main phospholipin component of the complex is not essential for the manifestation of antigenic properties. More thorough treatment with formamide gives rise to complete dissociation of the remaining polysaccharide-protein complex, and it was possible by this means to obtain for the first time a specific polysaccharide in its native or undegraded

condition. The polysaccharide obtained by this method ($[\alpha]_{5461} + 85^\circ$; N, 1.7%) is highly viscous in aqueous solution, contains a significant amount of organic phosphorus (0.5–1%), but fails to induce the formation of specific agglutinins, precipitins or protective immune-body in the rabbit. The observation was made that preparations of the polysaccharide in which only a few per cent. of the protein component ($[\alpha]_{5461} - 48^\circ$; N, 11.5–12.5%, P, 0.8–1.0%) remain are quite strong antigens, and it is essential, therefore, to establish beyond doubt that bacterial polysaccharide preparations are completely free from protein before concluding that the specific polysaccharides themselves are antigenic. The action of trypsin on the complete antigen has made it possible to isolate the phospholipin-polysaccharide part of the complex; this was found to be without significant antigenic properties. Similar observations were made by Freeman & Anderson (1941) for *Bact. typhosum*.

There is evidence which indicates that the native antigenic complex, as it exists in the intact bacterial cell, contains substances other than the phospholipin, polysaccharide and protein components, but it would appear from the dissociation experiments just described that, for some somatic antigens at least, the protein and the polysaccharide components are the two constituents whose presence is essential if the resulting complex is to possess the power to give rise to an immune-body specific for its polysaccharide component.

By utilizing the action of dilute alkali or 90% phenol on the native phospholipin-polysaccharide-protein antigen isolated from *Bact. dysenteriae* (Shiga) and *Bact. typhosum*, Morgan & Partridge (1941, 1942) obtained evidence that the protein component, which is toxic for animals, contains a prosthetic group and is, therefore, a conjugated protein. A similar conclusion has been reached by Freeman (1943), who has obtained a protein substance from the O-somatic antigen of *Bact. typhi-murium*. Observations (Morgan, unpublished) of the same kind have been made for the composition of the whole antigen complex and for the protein component of the O-somatic antigens of the various types of *Bact. dysenteriae* (Flexner). The true nature of the prosthetic group is not known. These results indicate that certain groups of bacteria possess somatic antigens which are built up from similar types of molecules arranged together as polymolecular aggregates. According to Morgan & Partridge (1940), each antigenic complex consists of a polysaccharide that is specific for the organism and responsible for its characteristic serological reactions, and a conjugated protein component which endows the polysaccharide with antigenic properties. Other components of the native antigenic complex such as the phospholipin, are also present but are not essential for the manifestation of antigenicity. Further unidentified substances are possibly also present in the native antigen.

Considerable support for this conception of antigenic structure was obtained when it was observed by Partridge & Morgan (1940) that the isolated, undegraded and non-antigenic specific polysaccharide component of the O-antigen of *Bact. dysenteriae* (Shiga) could be re-combined with the non-specific conjugated protein of the native antigen to yield an antigenic complex that would give rise to antibodies which are specific for the polysaccharide component, and thus for the homologous organism. It was also found that specific somatic polysaccharides obtained from organisms belonging to the dysentery-typhoid group combine readily with the conjugated protein component derived from the corresponding somatic antigen of another organism within the group, and that the artificial antigen so formed induces the formation of a specific immune-body for the polysaccharide component. Further evidence which supports

these views on antigenic composition is provided by the success with which certain non-antigenic polysaccharides, such as agar, gum acacia, and cherry gum (Partridge & Morgan, 1942) or the specific blood-group A or B haptens of animal or human origin (Morgan, 1943a, 1943b; Morgan & King, 1943; King & Morgan, 1944 and unpublished observations) have been converted to full antigens by combination with the reactive bacterial conjugated protein mentioned above.

The polysaccharide component of the "Shiga" antigen contains *d*-galactose, *l*-rhamnose and N-acetylhexosamine (Morgan, 1938) whereas the corresponding hapten from *Bact. typhosum* is built up from molecules of *d*-glucose, *d*-mannose and *d*-galactose (Freeman, 1942). The main phospholipin component of the O-antigen of *Bact. dysenteriae* (Shiga) yields α -glycerophosphoric acid, oleic acid and palmitic acid on saponification with alcoholic potash, and is similar in certain of its properties to cephalin rather than lecithin (Morgan & Partridge, 1940).

The nature of the antigenic complex of another Gram-negative organism, *Br. melitensis*, has been considered in detail by Miles & Pirie (1939), who have employed a different method of approach from those already described. Suspensions of *Br. melitensis* in chloroform water or dilute phenol (2%) were found to give up their specific antigen, which could be recovered from solution by differential sedimentation. Further fractionation of the material with ammonium sulphate gave rise to viscous opalescent solutions of the material that showed anisotropy of flow. Certain lipid components of the complex were readily removed by treatment with organic solvents and protein-like material was eliminated by treatment with acetic acid. Gentle hydrolysis of the antigen gave rise to a formyl derivative of an aminopolyhydroxy compound and an insoluble phospholipin. The formyl derivative of the polyhydroxy compound is an inhibitory hapten, but loses this power with the disappearance of a phospholipin group, on further hydrolysis; this component is neither toxic nor antigenic. Preparations of the antigen in different states of aggregation differ in antigenicity, toxicity and immunizing power.

General Conclusions

The steady increase in our knowledge of the chemical nature of bacterial antigens is likely to lead to the preparation of these biologically important complexes in a form which is free from non-specific substances and therefore more suitable for prophylactic immunization than the crude bacterial suspensions that have so far been employed. A beginning has already been made, and the extracted and purified O-somatic antigen of *Bact. dysenteriae* has been employed for the immunization of man against infection with this organism (Morgan & Schütze, 1943). Ultimately, when the exact nature and function of the component parts of antigens that have been derived from pathogenic bacteria are known, it may be possible to synthesize, by the methods of organic chemistry, hapten molecules of relatively simple composition. These might be combined with a suitable protein component and used to induce the formation of immune-bodies that will function therapeutically with an efficiency equal to the more highly specific antibodies that are produced by immunizing with whole organisms. Progress along these lines has also been made by Goebel (1939). The old adage "prevention is better than cure" is surely the right approach to the problem of the control of infectious disease, and we may anticipate with confidence the successful use of purified preparations of natural antigens or of artificial antigenic complexes built up from natural or synthetic haptens for the purpose of establishing an effective immunity in man.

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556

THE NATIONAL COLLECTION OF TYPE CULTURES

R. ST. JOHN-BROOKS, M.D.

Curator, National Collection of Type Cultures

With the insistent growth of microbiology from the pioneer days of Pasteur and Koch and the "Golden Age" of bacteriology, the need for type-culture collections of micro-organisms has continually been present in the minds of workers in the various fields, both for the study of principles and methods in microbiological investigation, and for the systematic classification of bacteria in their various species and strains.

Before the war of 1914-18, the principal sources of supply available for microbiologists were the collection of the American Museum of Natural History in New York, the Kral Collection in Vienna and the Collection of the Pasteur Institute in Paris. In addition to these, there were what might be called specialist collections, mostly on the continent of Europe, such as the *Centraal-bureau voor Schimmelcultures* at Baarn, Holland, and the associated *Laboratorium voor Microbiologie* at Delft, the Collection of the *Carlsberg Laboratorium* at Valby, near Copenhagen, which concerned itself with the maintenance of yeasts, and the Collection of the *Institut für Gärungsgewerbe* in Berlin. It is a matter for regret that the Carlsberg and Kral Collections have disappeared under the stress of economic pressure. The American Type Culture Collection, enlarged and reconstituted, is at present domiciled at the Georgetown University Medical School in Washington, D.C. under the curatorship of Professor Mario Mollari. In Rio de Janeiro a noteworthy collection of micro-fungi is maintained by Dr. O. da Fonseca at the *Instituto Oswaldo Cruz*.

Foundation of the Collection

In the early years of the present century there was no representative collection of micro-organisms in Britain, but in the year 1920 the *National Collection of Type Cultures* was founded under the joint control of the *Medical Research Council* and the *Lister Institute of Preventive Medicine*, who had long contemplated the formation of such a collection from which microbiologists in general and bacteriologists in particular might obtain from a trustworthy source authentic strains of recognized micro-organisms for use in scientific work. The *Lister Institute* provided, and continues to provide, accommodation and the necessary amenities, while the *Medical Research Council* bears the expenses of administration and of any special equipment that may from time to time become necessary.

The unit was formed under the general direction of the late Sir John Ledingham, F.R.S., then Chief Bacteriologist to the *Lister Institute*. He retired from the directorship of the Collection in 1930 on his appointment as Director of the *Lister Institute*, since when the Curator—the author of this article—has acted as chief executive officer.

The nucleus of the Collection was formed from the private collection of the *Lister Institute* of some few hundred strains, which included the valuable collection of anaerobic bacteria

(*Clostridia*) of Dr. Muriel Robertson, and the yeast collection of the Nobel Laureate—the late Professor Sir Arthur Harden, F.R.S. It has grown steadily from year to year, and has been enriched by donations from many sources. Among these may be mentioned over 150 separate species or subspecies of food-poisoning organisms belonging to the genus *Salmonella* received from Dr. H. Schütze (*Lister Institute*), Dr. Fritz Kauffmann (University of Lund, Sweden) and Dr. P. R. Edwards (Agricultural Experiment Station, Lexington, Kentucky, U.S.A.); *Aspergillus* and *Penicillium* species from Dr. Charles Thom and Dr. Kenneth Raper (U.S. Department of Agriculture) and from Professor H. Raistrick, F.R.S. (London School of Hygiene); collections of sporing aerobic bacteria (*Bacillus*) from Dr. W. W. Ford (Johns Hopkins University, Baltimore), Dr. Nathan Smith (Department of Agriculture, U.S.A.) and Dr. T. Gibson (Edinburgh and East of Scotland College of Agriculture); pathogenic fungi of interest in medical mycology from Sabouraud's collection through Dr. J. T. Duncan (London School of Hygiene) and from Dr. Roger Baker (Duke University School of Medicine, North Carolina, U.S.A.); grouped strain of *Pasteurella* from Dr. J. T. Cornelijs, and of *Bacterium pseudotuberculosis-rodentium* from Dr. H. Schütze; a collection of viruses of human and animal origin from Dr. E. W. Hurst (*Lister Institute*); *Streptococcus pyogenes* types from the late Dr. F. Griffith (Ministry of Health); American pneumococcus types from Dr. R. S. Muckenfuss (Rockefeller Institute, New York) and English types from Dr. M. Y. Young (*St. Mary's Hospital*) through Sir Alexander Fleming, F.R.S.; soil organisms from Dr. H. G. Thornton, F.R.S. (Rothamsted Experimental Station) and Dr. S. A. Waksman (Agricultural Experiment Station, New Jersey, U.S.A.) and representatives of Gardner and Venkatraman's *Vibrio*, groups I to VI, from Professor A. D. Gardner (School of Pathology, Oxford).

Work and Personnel

In the first year of the Collection's existence over 1,500 cultures were distributed to workers at home and abroad. This figure increased steadily from year to year, so that by the last academic year before the present war the number sent to correspondents throughout the world had reached a total of over 6,400 strains. Of these some 45 % were issued for purposes of scientific research, 20 % to colleges and schools for teaching purposes, and 35 % in connection with technology. The Collection now comprises some 4,000 strains of micro-organisms, consisting of about 1,400 separate species. Of these about half are bacteria—the remainder fungi, yeasts and associated organisms. Large numbers of strains of micro-organisms are lodged year by year for purposes of maintenance or investiga-

tion. The struggle in which we are still involved has sadly curtailed overseas activities, as can well be imagined, but the demand for cultures in the British Isles has, apparently, been stimulated by war conditions and the staff has been very fully occupied, in spite of temporary isolation from many European and other colleagues.

The personnel of the Collection consists of a Curator, Assistant Curator and technician with the necessary laboratory assistants—the whole under the general direction of the *Medical Research Council*, of which the present Director of the Lister Institute—Dr. Alan N. Drury, F.R.S.—is a member. The Collection is a general one, but plans are in the making which will to some extent modify its structure in the post-war years and make it more adequate to serve the special needs of research workers in medical and veterinary bacteriology. Nevertheless, though at the present time the medical and veterinary aspects of the Collection are particularly stressed, the needs of agriculture, technology and teaching are well catered for—indeed the Collection on its present basis is of service to all workers in the various disciplines of microbiology.

The Collection also acts as a useful repository for important strains, which the original investigator, for one reason or another, cannot maintain. Examples of these in the National Collection are numerous yeast cultures formerly preserved at the *Carlsberg Laboratory*; a collection of *Actinomyces* species from Jamaica, which are antagonistic to the growth of *Fusarium oxysporum* var. *cubense*—the causal organism of Panama disease of bananas; as also a series of organisms (*Acetobacter*) isolated from vinegar brews in East Africa. These examples serve to indicate the varied material with which the Collection has to deal and the diversity of places from which it originates. Attention is directed to the continued need for the deposition of newly described species and also for fresh examples of familiar types. It is only by constant augmentation and replenishment of such material that the requirements of workers at home and abroad in the various disciplines of microbiology can adequately be satisfied. The co-operation of microbiologists is earnestly invited and in return every effort is made to supply the needs of applicants for cultures. The staff is always glad to help correspondents in the identification of material and cultures, which should be accompanied by the fullest particulars as to source and date of isolation and, if possible, by clinical and epidemiological notes. Cultures are supplied on demand, so far as possible, to workers throughout the world. A small charge is usually made to help to defray the cost of materials and postage.

A new edition of the Catalogue of the National Collection is at present in preparation and will be issued as soon as circumstances permit after the war. In addition to the catalogue, a list of fungi maintained in the Collection is printed from time to time in the *Transactions of the British Mycological Society*. The staff of the Collection is in close touch with widespread activities. For example, the Curator has acted in an executive capacity at the Paris, London and New York Congresses for Microbiology and is at present serving as Secretary of the Permanent International Commission, the Nomenclature Commission and the Salmonella Sub-committee of the International Association of Microbiologists. The staff, in addition, is actively interested in problems of medical mycology and in the formulation of the proposed rules of bacteriological classification.

In addition to the routine subculture of numbers of strains, on appropriate media, cultures are also kept as desiccates, whenever possible, thereby preserving their biological characters unaltered for many years. For some considerable time a simple but effective technique of "snap-freezing", devised by Professor Alfredo Sordelli of Buenos Aires, has been employed. This method is of value in the preservation of small quantities of material. It consists of rapid evacuation with a Hyvac pump, trapped with phosphorus pentoxide, avoiding the lethal effects of concentration and aggregation of protein molecules in the process of desiccation, which leads to their denaturation. The necessity of employing a special freezing agent, such as "dry ice", is thus eliminated.

All organisms listed in the catalogue of the Collection are maintained at the Lister Institute, Elstree, Hertfordshire, where the Collection was removed, from London, on the outbreak of war, with the exception of fungi causing disease or spoilage of timber, which are the special care of the Forest Products Research Laboratory at Princes Risborough, and most of the filterable viruses and bacteriophages, which are

obtainable in certain cases from specialists in the various groups. Thus a start has been made in a process of decentralization which will be referred to later.

Future Development

With regard to the general question of the future of type-culture collections, two lines of development are possible. The maintenance of large general collections presents increasing difficulties of administration and, with ever-expanding knowledge in the various fields of microbiology, it will become more and more difficult to maintain such collections under the direction of a small, even if devoted, band of workers. Such a staff may, and indeed often does, possess a wide knowledge of microbiology in all its aspects, but cannot possess intimate specialized knowledge of all the groups comprised in a large general collection; nor are the laboratory facilities usually sufficient for the extensive and minute examination and periodic overhaul of such an expanding collection. Short of an Institute of Microbiology, with ample funds, staff and accommodation, there is not much hope for expansion in this direction. Nevertheless the idea is not without attraction. The growing interdependence of the various branches of microbiology has been stressed recently in Britain by the formation of a new Society—The Society for General Microbiology—which has received influential support from every field of microbiology.

A second line of development is more immediately hopeful. In place of the large general collection, kept to serve the ordinary requirements of microbiologists, it is suggested that a greater measure of decentralization than at present employed should be introduced. Responsibility in respect of a number of groups of organisms might be delegated to appropriate specialized reference laboratories (many of which already exist in connection with the Emergency Public Health Laboratory Service formed under the aegis of the *Medical Research Council*), while a limited selection of "tested cultures" for use in medical and veterinary teaching would be kept under constant supervision at headquarters. While retaining a nucleus to meet the needs of routine and teaching purposes, the present collection might well act as a central bureau or clearing house and be in close association with specialist correspondents in the various groups who would undertake to supply cultures on request. Such a system need not be costly, but would require much careful organization.

International Collaboration

To take the broader aspect of international collaboration and reciprocity one may envisage at some future date the formation of an International Commission or International Advisory Committee on Culture Collections, sponsored in all probability by the International Association of Microbiologists, whose activities, exemplified by its Paris, London and New York Congresses, have unfortunately been interrupted by the war. Much good work in the international sphere has been delayed by the impossibility of holding the Fourth International Congress in Copenhagen in 1942, as arranged. The international character of such an organization might be developed through official and unofficial agencies in the different countries concerned, the objects of such an organization being briefly as follows:

To make more adequate provision for permanent reservoirs of collections of living micro-organisms (including bacteria, protozoa, micro-fungi, micro-algae and viruses), particularly those of importance in medical, veterinary, agricultural and industrial science.

To provide more effectively for the needs of workers in fundamental biological studies, such as genetics, cellular physiology and biochemistry.

To develop new facilities in continental areas not at present adequately served and to expand the scope and utility of existing culture collections.

To promote international co-operation and integration in these respects through appropriate channels.

It is becoming increasingly evident that international scientific co-operation has received an immense stimulus as a result of the pooling of information during the present war. Moreover, increased facilities for rapid communication provided by modern air transport will, in the future, greatly expedite the interchange of scientific material and information. In this dissemination the various type-culture collections will

surely take part—an immediate need to be filled being the share they will take in the scientific rehabilitation of the countries that have been ravaged and impoverished by war, by supplying type cultures for comparison with others and for fundamental scientific research.

It appears, therefore, expedient to have some kind of "blue-

print," as outlined above, in readiness for the days to come. If in the future a scheme of this character should be evolved, it would, without doubt, help to promote mutual good will and understanding among the best elements of the various nations, and contribute effectively to that reciprocity in microbiological science which is so greatly to be desired.

REVIEW OF SELECTED PAPERS

Influenza

557

STUDIES ON AIR-BORNE VIRUS INFECTIONS. III. The Killing of Aerial Suspensions of Influenza Virus by Hypochlorous Acid

by D. G. ff. Edward & O. M. Lidwell, *Journal of Hygiene*, 43, 196-200, September 1943

The possibility of destroying influenza virus by aerial disinfection is perhaps of particular interest at the present time. It has been found by Andrewes (1940) that aerosols of influenza virus could be rendered non-infective by sodium hypochlorite mists; Drs. Edward and Lidwell, also working at the National Institute for Medical Research in London, have now given details of experimental findings. The influenza-virus suspensions used were prepared from the lungs of mice which had been infected with the PR8 and W.S. strains. In 4 of 5 experiments in which virus aerosols were in contact with hypochlorous acid gas in concentrations of from 1: 640,000 to 1: 3,000,000 for 20 minutes, 99 % of the virus was destroyed. The virus aerosol was as easily killed by the gas as *Streptococcus salivarius*. Preliminary experiments on mice and cats failed to show any toxic effects produced by inhaling the gas in relatively high concentration for prolonged periods.

REFERENCE

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558

CLINICAL STUDY OF AN OUTBREAK OF INFLUENZA B DURING THE WINTER, 1942-43

by J. M. Stansfeld & C. H. Stuart-Harris, *Lancet*, 2, 789-790, 25/12/43

This paper records the clinical data of the outbreak described by Stuart-Harris, Glover & Mills (1943). The patients came from certain military units and had been admitted to camp reception stations with fever and acute respiratory infections, but not all were considered typical influenza. Records of 25 cases in an American hospital (in Britain) suffering from influenza-like illness were also available. Hirst serum tests were made on both acute and convalescent sera of all patients, and according to the rise of antibody to influenza B they were placed in three categories: (i) A significant (4-fold or greater) rise of antibody was obtained in 24 cases from the reception stations and in 11 cases from the American hospital; (ii) no rise in antibody could be detected in 14 patients from the reception stations, nor in 12 from the American hospital; (iii) four cases from the reception stations and 2 from the American hospital gave a 2- to 3-fold rise in titre. Sera from all cases in categories (ii) and (iii) and from 6 cases in category (i) were tested against virus A, but with negative results. The signs and symptoms of 24 of the cases of influenza B and 12 cases of influenza Y (those whose type of influenza was not determined serologically) were then compared with the signs and symptoms of 60 cases of influenza A studied during 1937-41. In addition to clinical data, radiological findings were available in 20 cases, and leucocyte counts in all 25 cases in the American hospital.

The conclusion reached from a comparison of cases of influenza A, B and Y was that the three differed little in the incidence of general aching or coryza, although the average maximum temperature was a little lower in the B group. It

has been suggested by Taylor, Parodi, Fernandez & Chialvo (1942) that clinical differences may be detectable between influenza caused by virus A and by virus B, but the present authors found that the two groups were indistinguishable.

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² [see *BMB* 559]

559

INFLUENZA IN BRITAIN, 1942-43

by C. H. Stuart-Harris, R. E. Glover & K. C. Mills, *Lancet*, 2, 790-793, 25/12/43

During the winter and spring of 1941-42 and 1942-43 workers at the National Institute for Medical Research, London, and at a military laboratory, have continued to study the changing character of recent influenza epidemics in Britain. In 1941-42 Hirst serum tests were made on 52 sporadic cases of clinical influenza and atypical pneumonia, but the results were entirely negative. A few garglings were also examined from military units, but ferrets could not be infected with this material and it was concluded that no influenza-virus infection of known type was current during this period. During 1942-43 an investigation of acute respiratory infections was carried out in two divisions in which cases were officially notified (Stansfeld & Stuart-Harris, 1943). In division B, the cases were divided into febrile and afebrile, but in division A they included all cases of colds, sore throat, influenza, bronchitis and pneumonia, whether febrile or not. The incidence of respiratory infection was low in both divisions but sporadic cases of influenza occurred in some regiments.

During the entire period in division A, and from January to March in division B, tests were made on garglings and on the sera collected from cases of upper respiratory-tract infections. The entire series of serological tests in 1942-43 was made with reconstituted dried allantoic fluid and Hirst's (1942) new technique was used. Of 114 sera tested against virus B, 52 showed no change, a decrease in titre, or an increase not exceeding 1½-fold; 12 showed a 2- to 3-fold increase, and 50 showed an increase of 4-fold or greater. The sera of all 52 in the first category, of 11 in the second, and of 15 in the third were also tested against virus A. Only 2 pairs of sera showed differences in titre with virus A in excess of 3 times; the majority showed no change. These results were interpreted as indicating infection with influenza-virus B in 50 patients. It was noted that the rise of B-antibodies in individual patients was correlated with the initial titre of the serum, so that patients with low initial levels of antibody more often showed increases than those with high initial levels.

Towards the end of the normal influenza season, and after it, there was a number of small outbreaks apparently due to influenza A. Two or three cases of influenza at the end of March showed increase of antibody to influenza A but not to B. Further localized outbreaks in March and again in May and in June 1943 were also found to produce significant rises in titre against virus A.

Attempts were made to recover, by means of egg-inoculation, strains of influenza virus from garglings of the patients who did, or did not, show increases in B-antibody. The

garglings were filtered and inoculated amniotically into 12-day chick embryos, but the results from 21 patients were negative. Garglings from 26 patients were inoculated intranasally into ferrets between January and April 1943 and the results, at first, were entirely negative. However, in 8 ferrets inoculated with the original material there was a 4- to 16-fold increase in the blood level of antibody against B-virus. The specificity of the antibody in the ferret sera was confirmed in 5 instances by neutralization tests in mice. It was possible to make a comparison between sera from human cases and sera from ferrets inoculated with the corresponding garglings in 21 instances. In 7 cases, both human and ferret sera were negative: in 6, both were positive; in the remaining 8, the human sera were positive, and the ferret sample was negative.

Recent serological tests (Lush, Stuart-Harris & Andrewes, 1941) have shown that a considerable proportion of cases of influenza towards the end of 1939 was due to B-virus. This was the first record of this strain in the British Isles. In 1940-41 there were mild outbreaks, some of which were due to A-virus. During the early months of 1942 there were no widespread epidemics and no evidence of infection with virus A or B was obtained. Towards the end of the year, however, and again in January and February 1943, a mild increase of acute respiratory infection was associated with serological evidence of influenza-virus B infection. Clinically the illnesses were typical influenza, but other respiratory infections which did not evoke the serological evidence for known influenza viruses were also occurring at the same time. Subsequently, from March to June, the type of infection changed again and minor outbreaks of influenza A infection occurred in the country. Later on, in November 1943, influenza appeared in epidemic form and the virus responsible was of the A type. This course of events bears some similarity to the Argentine records for the years 1940-42 (Taylor, Parodi, Fernandez & Chialvo, 1942).

Finally, the authors discuss the value and limitations of the Hirst technique in detecting virus-B infections. Provided that the factors causing variation in the inhibition titres of any particular serum are fully recognized and suitable precautions are taken (Stuart-Harris, 1943), the test is exceedingly useful. The authors confirm the findings of Taylor *et al.* (1942) on the value of instilling garglings into ferrets and subsequently examining the animal's serum by the Hirst technique. Serial passages through ferrets were also found to induce a rise in antibody, although no overt symptoms of infection could be recognized.

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¹ [see *BMB* 558]

560

INFLUENZA "A": AN ACCOUNT OF A MINOR EPIDEMIC

by T. H. Donnelly, H. P. Hughes, D. Robertson & E. Philipp, *British Medical Journal*, 1, 42-43, 8/1/44

This account, by medical officers of the Royal Air Force and Royal Australian Air Force, gives clinical and pathological details of an outbreak involving 68 cases at an airfield. A Canadian airman went sick with symptoms of influenza on March 30, 1943; thereafter single cases occurred on April 3, 14 and 16. Ten cases were reported on April 21 and it then appeared obvious that an epidemic was developing. On April 23 some of the 30 patients then in sick quarters were examined by: (i) chest radiography; (ii) differential blood count; (iii) throat swabs; (iv) blood culture; (v) sputum examination; (vi) titration of antibodies in the blood against influenza viruses A and B. In most cases headache was severe, there was slight soreness of the throat, nasal catarrh, nausea and low backache. Temperatures varied between 102° and 103° F. [about 39°-39.5° C.]. There was little of diagnostic value in the blood counts, throat-swab examinations, or blood cultures. Sputum examinations disclosed one case of pulmonary tuberculosis,

but otherwise were negative. Only one case showed radiologically congestion and some consolidation of the right base. Titrations of antibodies in 6 cases against influenza viruses A and B by the Hirst technique showed no significant change in antibody level against virus B, whereas 4 showed a good rise (6- to 16-fold) against virus A. It is suggested that some of the cases which showed no increase of A-antibodies may already have had good A-antibodies in the serum and the infection may have failed to cause a further rise (Andrewes, 1942). The authors discuss the methods of treatment of such an epidemic and consider that sulphapyridine was useful in preventing subsequent pneumococcal or streptococcal infections. They also emphasize the importance of bearing influenza in mind when patients develop unusual symptoms, and they point out that failure to do so may mean the introduction of influenzal infection into hospitals.

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¹ [see *BMB* 65]

561

THE INFLUENZA "A" OUTBREAK OF OCTOBER-DECEMBER, 1943

by C. H. Andrewes & R. E. Glover, *Lancet*, 2, 104-105, 22/7/44

During the last three months of 1943 there occurred in Britain the most widespread outbreak of influenza since 1937. A small number of cases of influenza in the early months of the year was found to be due mainly to influenza-virus B; but in April localized and small outbreaks caused by virus A began to be observed. Sera from patients involved in the main outbreak were examined by workers at the National Institute for Medical Research in London and subjected to the Hirst test—the titration in sera of the property of inhibiting the agglutination of fowl erythrocytes by influenza virus. Serum samples were taken from clinically typical patients early in the disease and again 10-14 days later. Using a 4-fold rise in titre as significant of infection, 72% of the 60 sera examined were positive for virus A, while if a 2-fold rise in titre was taken as significant 82% had been infected with virus A. No rises in titre against influenza-virus B were found.

In addition to the Hirst tests, unfiltered garglings from 24 patients were inoculated into ferrets and typical symptoms were produced with 14 of the specimens. Material from most of the positive or doubtful ferrets was passed intranasally to more ferrets by inoculating ground suspensions of lung and turbinates, or nasal washings. The latter were obtained by allowing the anesthetized ferret to breathe for 30 seconds with its nose intermittently under the surface of 5 cm.³ of broth in a Petri dish (Burnet & Bull, 1943). This gave material for passage while allowing the animal to be kept for serological study. In contrast to results obtained by the authors in the previous few years, garglings inoculated into ferrets either produced definite symptoms and virus was readily transmitted in series, or the tests were unequivocally negative.

Adaptation to mice was attempted in 17 instances from the ferret material of 9 of the strains. After 2-6 ferret passages, pooled lung- and turbinate-suspensions were inoculated intranasally into mice without filtration, and at least 4 serial passages were carried out. Only 2 of the strains could be adapted in this way, despite various expedients to improve on these results. Adaptation to chick embryo was attempted with filtrates of 4 garglings which were inoculated amniotically into 10-day chick embryos. Virus was then sought for by Hirst tests on amniotic and allantoic fluid, but without success.

If it can be assumed that the material available for the present study was representative of that to be found in the country generally, it seems that the October-December 1943 outbreak was due to influenza-virus A. Influenza of a similar type occurred in the U.S.A. in the autumn of 1943, and it is noted that, there also, the epidemic was preceded in the spring by small outbreaks due to A-virus. The ease with which ferrets could be infected supports Andrewes' (1942) contention that there may be a correlation between the extent of epidemic spread in man and the ease with which laboratory animals can be infected. This theory, however, was not

borne out so far as mice were concerned. The authors draw attention to their lack of success in infecting chick embryos with human material and suggest that the breed or diet of the fowls providing the eggs may be important.

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¹ [see BMB 65]

562

INFLUENZA VIRUS AS A LABORATORY CONTAMINANT

by C. H. Andrewes, R. E. Glover, F. Himmelweit & W. Smith, *British Journal of Experimental Pathology*, 25, 130-134, August 1944

It is not generally recognized that viruses can act as contaminants in much the same way as bacteria. Recently-developed techniques, such as the blind passage of material from one animal to another, increase the chances of such contamination: a trace of virus accidentally introduced during passage may make its appearance after one or two further passages. Workers in the National Institute for Medical Research (Hampstead) and at St. Mary's Hospital, London, were led to investigate this possibility by two incidents which occurred during the course of their own work and the evidence they present is highly suggestive.

The W.S. strain of influenza virus, originally isolated by the Hampstead workers in 1933, is antigenically distinct from the vast majority of A strains, and in addition it has other biological peculiarities. Since 1933, no W.S.-like strain has been shown to be the agent responsible for an outbreak of influenza. Yet W.S. virus has made its appearance in various laboratories under the following circumstances: (i) Worker A in country Z recovered an influenza A strain serologically like W.S. from an outbreak. The strain was, at the time, the only one known to have been isolated by this worker. The Hampstead laboratory had previously sent W.S. virus to A. (ii) Worker B in country Z also recovered a W.S.-like strain from an outbreak and he too had previously been sent the W.S. strain. (iii) Worker C in country X recovered a single strain of the W.S. type from an outbreak. None of the numerous strains recovered by other workers from the same outbreak was like the W.S. strain. W.S. virus had previously been sent to C. (iv) Worker D in country Y recovered W.S. virus from normal mice, although other workers have failed repeatedly to do so. W.S. virus had been previously sent to D. (v) Worker E in country W recovered the only strain known to have been found by him from an influenza patient. This strain was identical with the W.S. strain previously supplied to him. (vi) Worker F in country V recovered several strains of influenza from normal carriers although other workers have failed to do so. One of these strains proved to be exactly like the W.S. virus previously sent to him.

In addition to this evidence, certain happenings in the authors' own laboratories strengthened their suspicions. W.S. virus, for example, was recovered from vaccinia virus which was being used to infect mice; a different strain of virus sent to a worker G was found to be contaminated with W.S. virus after a few mouse-passages; another worker recovered the W.S. strain after a few passages in mice from material from a sufferer from the common cold. At the time of all of these incidents, W.S. virus was under study in the laboratories concerned. Three further accidents of a similar nature also occurred in the same laboratories at a time when the influenza-virus strain PR8 was under study. In these three cases the contaminating organism was the PR8 strain.

In view of the possible transference of influenza infection from mouse to mouse within a cage, or from cage to cage, experiments were undertaken to determine whether this was a possible explanation of virus contamination. An attempt was made to confirm the experiments of Eaton (1940) who had shown that influenza could spread readily from mice infected with heavy doses of virus. The early experiments seemed to confirm the American work, but later it became much more difficult to demonstrate spread of the virus

among mice. In any event, infection of normal stock is unlikely to explain the contamination since laboratory infection does not spread from one mouse jar to another.

While it is possible that some of the 14 instances described in this paper may be explained on other grounds than as contamination, the evidence presented is very suggestive. It seems that influenza virus may appear as a laboratory contaminant under conditions not yet understood. The important implications of this work are obvious, and the authors make the useful suggestion that, where a strain of virus is recovered under unusual circumstances, it should be stated whether stock strains of the particular virus have or have not been recently under study in the laboratory concerned.

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Poliomyelitis: Vaccinia

563

POLIOMYELITIS: EXPERIMENTAL WORK IN EGYPT
by C. E. van Rooyen & A. D. Morgan, *Edinburgh Medical Journal*, 50, 705-720, December 1943

During the years 1941 and 1942, 106 cases of poliomyelitis occurred among troops of the Middle East Forces, and of these 33 died. The present paper by two British Army pathologists gives clinical and histological details of 7 of the fatal cases together with an account of the methods adopted in demonstrating the infecting virus.

The lesions encountered were in the main similar to those found in England except that they were more extensive and severe. While the severity varied at different levels, pathological changes were usually found throughout the length of the cord. The anterior horn cells showed swelling, loss of outline, chromatolysis and karyolysis, only an occasional cell at the periphery of the grey matter escaping. Infiltration with polymorphs and lymphocytes (the former predominating in fulminating lesions) was observed throughout cross sections of the grey matter. It was noted that while almost all cases died of medullary failure extensive lesions were usually found as high as the pons and mid-brain and even in cases showing nothing but bulbar paralysis slight lesions could be found as low as the lumbar enlargement.

The experimental animals employed in the study were the Sudanese monkey, *Cercopithecus aethiops*, and the Abyssinian baboon, *Papio hamadryas*. The latter species was found to be highly susceptible to the disease. Segments of spinal cord from fatal cases of poliomyelitis were emulsified in glycerol saline of pH 7.2, allowed to stand for 3 days and then tested by aerobic and anaerobic culture for viable bacteria. Thereafter a 1:20 emulsion of the tissue was prepared, centrifuged at 3000 revolutions per minute for 30 minutes, and 0.25 cm.³ of the supernatant fluid was inoculated intracerebrally. By this technique poliomyelitis virus was demonstrated in 6 of the 7 fatal cases, the animals usually dying in from 5-8 days with the typical clinical and histological features of poliomyelitis. In view of the ease with which the disease could be induced in *C. aethiops* an attempt was made to test the prophylactic and curative effect of sodium sulphadiazine in experimental infections. The drug had no appreciable effect on either of the two monkeys used.

In addition to known cases of poliomyelitis, a small number of neurological cases in which the clinical signs were suggestive either of choriomeningitis, encephalitis, or brachial neuritis were also investigated. Tests were made at the Rockefeller Institute for Medical Research to ascertain whether the sera of these patients contained neutralizing antibodies against a number of known virus infections. The sera from 9 out of 11 of these cases gave positive protection when subjected to the Lansing-strain poliomyelitis-virus intracerebral mouse-protection test. A control experiment with sera from normal

troops would have enhanced the value of these observations. The authors conclude this paper by noting the striking difference in the incidence of poliomyelitis among the troops compared with that among the civilian Egyptian population. According to available evidence only 11 cases of poliomyelitis occurred in Egypt during the years 1938 and 1939.

564

POLIOMYELITIS IN BRITISH AND AMERICAN TROOPS IN THE MIDDLE EAST: THE ISOLATION OF VIRUS FROM HUMAN FAECES

by J. R. Paul, W. P. Havens & C. E. van Rooyen, *British Medical Journal*, 1, 841-843, 24/6/44

The present report, by pathologists of the American and British Forces, is mainly concerned with attempts to isolate virus from the stools of typical and borderline cases of poliomyelitis which occurred among troops stationed in Libya, Egypt and Palestine. They sought to establish the local value of the procedure in diagnosis, and to find out whether adult sporadic cases harbour the virus in the intestinal tract in the same way as juvenile cases do in areas where the disease is epidemic. Not much help was obtained in explaining the extreme severity of the type of poliomyelitis met with by studying the published information about the disease in the countries concerned. Only 13 cases were officially recorded for the years 1938 and 1939 in Egypt, but unofficial records suggest that poliomyelitis was not uncommon especially among children under 5 years of age. Records also suggest that it is not rare in Palestine, especially among Jewish children.

Among British troops 74 cases occurred in 1941, with 19 deaths, while in 1942 there were 32 cases with 14 deaths. The rate among American troops in the Middle East during the first 10 months of 1943 was more than 10 times that recorded in the U.S.A. for a similar period. Attempts to obtain an epidemiological link between 10 of the military cases and cases occurring among the civilian population were unsuccessful; the military cases were ubiquitous in their place of origin and no two patients seemed to have been in contact.

The advantages of testing stools rather than nasopharyngeal washings in poliomyelitis rest on the fact that in juvenile cases the virus remains in the intestinal tract for some 20 days whereas it is present for only 2 to 4 days in the nasopharynx. Information about the presence of virus in the stools of adults, however, is incomplete. Stool specimens from 35 patients and contacts were tested: 17 of these were American and 18 British. Five types of case were studied: (i) 15 typical cases of poliomyelitis, 10 of which were fatal; (ii) 5 cases diagnosed as polio-encephalitis; (iii) 6 cases diagnosed as acute benign lymphocytic meningitis; (iv) 6 cases of localised neuritis; (v) 3 poliomyelitis contacts.

Methods employed in demonstrating the virus were to keep stool specimens or enema material refrigerated not more than two weeks before preparing a 10% suspension in sterile distilled water and allowing it to settle at room temperature. The supernatant fluid was then divided and part was instilled in 3 cm.³ amounts into the nostrils of a monkey on three or four successive days. The second part of the fluid was immediately centrifuged and 15% ether was added to the supernatant and refrigerated for 48-72 hours before intraperitoneal inoculation in 15-20 cm.³ quantities into the same monkey. Five different species of monkey were used in these experiments: (i) grivet monkeys, *Cercopithecus griseoviridis*; (ii) Central African vervet monkeys, *Cercopithecus aethiops centralis*; (iii) small immature Abyssinian baboons, *Papio hamadryas*; (iv) Hussar monkeys, *Erythrocebus patas*; (v) the 'bonnet' monkey, *Macacus radiata*. The first four of these species were shown to be susceptible to poliomyelitis virus but the fifth was not adequately tested. In all, 44 monkeys were used, 6 of them twice.

Of the 15 poliomyelitis cases tested, the stools in 9 were shown to contain virus. Positive results were based on clinical signs, such as weakness and paralysis, and on histopathological evidence from the medulla and cord of infected animals. All patients from whom virus was obtained died. The results suggested that the amount of virus present in the intestinal tract was greater in the more severe cases of

poliomyelitis than in the milder cases. It is noted, however, that the faeces from the fatal cases were collected earlier in the course of the disease (from 3-10 days) than in the other cases. All tests for virus in the stools from cases other than typical poliomyelitis were negative.

565

ULTRAMICROSCOPICAL OBSERVATIONS ON THE MORPHOLOGY AND DEVELOPMENT OF VACCINIA VIRUS IN VITRO

by K. B. E. Merling, *British Journal of Experimental Pathology*, 24, 240-245, December 1943

The morphological appearances of living vaccinia virus in the corneal cells of rabbits have already been described by the author, who is a research fellow at the Bland-Sutton Institute of Pathology in London. In the present paper he reports a study of the life-cycle of vaccinia virus and describes survival of the virus *in vitro* in its various forms. The eyes of rabbits were scarified with the virus and, after keratitis had developed, thin tangential sections were cut with a sharp knife, while from the deeper layers scrapings were obtained with the blade of a knife. Control preparations from uninoculated eyes were also made. The material was placed in a drop of tyrode solution on a thin slide under a cover slip, which was sealed with paraffin wax. Observations were carried out at room temperature or on a warm stage at 37° C. using optical systems giving a high degree of resolution at the highest magnifications with dark-ground illumination. A number of photomicrographs of the more important findings are printed in the text and study of these is essential for appreciation of this article. It is not possible to describe these fully here, but the three forms of vaccinia virus which represent its life-cycle can be readily seen. Elementary bodies, discs and sphaeres together with secondary or daughter-cysts are illustrated. In some of the photographs of chain formations gaps occur and these are occupied by discs which are not recorded owing to their low brightness. No connecting filaments, as described by Paschen (1906) and Prowazek (1907) were visible. One photomicrograph shows the elementary bodies at a magnification of 2900, and clearly demonstrates their oblong shape. The resolution achieved in this photograph is remarkable because it is beyond the predicted possibilities of the Abbe and other image-formation theories of the microscope. The raising of the limit of resolution and of magnification was achieved by reducing the intensity of the light-source by polarized discs to such a degree as to produce coincidence between the minimum of photographic registration and the physiological thresholds of perception and differentiation of two light intensities.

Other figures illustrate large numbers of small colonies of virus which appear to have a very thin membrane holding their contents together. The small cysts are not round, as is the rule with those formed from cell extensions, but appear in a variety of shapes whose most impressive feature is change. On examining these cysts a week later, they appear to have grown to large dimensions, measuring 20 × 30 μ across their two diameters. The cysts may then stretch and divide into two or more, and following the division they may move across the field. Continuous small cysts are formed, grow and divide in seemingly endless repetition until about six weeks after the material is taken from the animal, when the process slowly comes to an end. It was noted that the formation of new colonies could take place after the complete disappearance of host-cells and of their broken fragments: evidently the metabolic products present in the liquid were stable and sufficient for the development of new colonies. Gradually, however, the cysts cease to be formed and the number of free-moving bodies also decreases. The end of the process of development of the virus in these specimens was immobilization with loss of brightness of the virus bodies. Control specimens of normal cornea kept for the same time showed cells in varying degrees of disintegration, but were negative for virus bodies.

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INCLUSION BODIES IN ASSOCIATION WITH TYPHUS RICKETTSIAE

by A. M. Begg, F. Fulton & M. van den Ende, *Journal of Pathology and Bacteriology*, 56, 109-114, January 1944

When typhus rickettsiae have become well adapted to a particular animal host, the organisms usually appear in the form of typical minute bacillary and coccobacillary forms; in smears from the tissues or exudates of infected animals the rickettsiae are to be found in large numbers in the cytoplasm of mononuclear cells as well as extracellularly. In this study by Begg and his colleagues at the National Institute for Medical Research, the appearances seen in the lungs of animals during the adaptation of rickettsiae to a new host-species have been followed.

Most of the observations were made on lung impression-preparations stained by Macchiavello's method. When the mouse-lung-adapted strain of the epidemic type (Breinl strain) was passed into the lungs of rabbits, no bacillary forms were found at first, but only small intracytoplasmic homogeneous inclusion bodies; with repeated passage, small granular inclusions, in some cases obvious small clusters of rickettsiae (morulae), began to appear in some cells; and in later animals, when the strain had become adapted to the rabbit and regularly produced consolidation of the lungs, rickettsiae were also found diffusely scattered in the cytoplasm of cells as well as extracellularly.

When mouse-lung-adapted rickettsiae of the murine type were passed into the lungs of rats homogeneous inclusion bodies were not found, but all stages described in the rabbit, from the morula onwards, were seen. Homogeneous inclusion bodies were not found in the lungs of mice at any stage of the infection with mouse-lung-adapted strains. However, while new strains from infected guinea-pig brain were being adapted to mouse lung, these inclusion bodies were easily found. As during adaptation to rabbit lung, the homogeneous inclusion bodies began to decline in number with the appearance of morulae and bacillary forms. The various forms described in lung preparations are beautifully illustrated by photomicrographs in colour. The authors believe that the homogeneous inclusion bodies occur only during adaptation of a strain of rickettsiae to a new host, and it is suggested that the morulae are more common when the invaded cell is somewhat resistant. While it appears that the homogeneous inclusions may be the most immature forms of morula, the authors consider that the evidence provided by ultra-violet photomicrography is rather against this view.

567

RICKETTSIAL AGGLUTINATION STUDIES IN TYPHUS FEVER

by C. H. Stuart-Harris, G. K. C. Rettie & J. O. Oliver, *Lancet*, 2, 537-538, 30/10/43

This work, by a group of army pathologists engaged in typhus research, affords further evidence of the value of agglutination tests with suspensions of typhus rickettsiae in this disease. The suspensions were prepared from infected mouse lungs, 3 strains of rickettsiae being employed. These were the Wilmington murine strain, the classical Breinl strain of epidemic typhus, and a strain isolated in 1942 by van Rooyen from a case of louse-borne typhus in Cairo.

Sera were examined from nine cases of louse-borne typhus fever which had occurred in the West of Ireland in 1942, as recorded by McConn (1943). The sera were obtained 2 to 5 months after subsidence of the fever. Significantly high titres of agglutinins to *Proteus* OX19 were present in the sera of 5 of the 9 cases and high OX2 titres in 2 of these and 1 other. Rickettsial agglutinins to the Cairo strain were present in 7 sera and 2 of these showed no agglutinins to the Breinl or murine rickettsiae. Five of the sera reacted with all 3 rickettsial strains; 4 of these showed a higher titre with the epidemic than with the murine organism, the fifth having similar titres with all 3 strains.

The authors note that, while sera from human cases of typhus fever usually showed both rickettsial and OX19 agglutinins, experimental infection of guinea-pigs and rabbits

produced sera which agglutinated rickettsiae but had either no, or only a weak, titre of agglutinins to OX19. A comparison of the results with sera from cases of typhus fever and from experimentally infected rabbits and guinea-pigs showed that, with human and rabbit sera, the titre of agglutinins for the infecting type of rickettsiae—epidemic or murine—was higher than for the other type, but that some cross-agglutination occurred in each case; with guinea-pig sera, however, the agglutinins tended to be specific for the infecting organisms. Cross-absorption of rabbit immune-sera with suspensions of rickettsiae of the 2 types supported other evidence that the 2 species of rickettsiae—*R. prowazeki* and *R. mooseri*—possess specific as well as a common antigen.

These findings together with the work of van Rooyen & Bearcroft (1943) and others suggest that rickettsial agglutination tests with the sera of typhus patients are more likely to indicate the nature of the infecting strain of rickettsiae than are Weil-Felix tests. The data available indicate that the cases of typhus in Ireland were due to *R. prowazeki*. The authors comment on the absence of a typhus epidemic from this part of Ireland since 1905, and speculate on the mode of survival of the organism in inter-epidemic times.

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¹ [see *BMB* 151]

568

ENDEMIC TYPHUS FEVER IN DIEGO SUAREZ, MADAGASCAR

by C. G. Baker, G. T. L. Archer & G. B. Mitchell-Heggs, *British Medical Journal*, 2, 506-508, 23/10/43

According to the local public health report for Madagascar in 1940, it was believed that the typhus group of diseases did not occur on the island. Major Baker and his colleagues in the Royal Army Medical Corps, however, have recorded in this paper a series of 10 cases which, in their clinical aspects, were typical typhus infections of mild or moderate degree of severity. The cases occurred among Service units in 1942. The clinical features of the illness are discussed and symptoms are tabulated. All 10 patients showed agglutinins in their serum to *Proteus* OX19 in dilutions of 1:200 or more, and in several of the patients in whom repeated examinations were made the agglutinin curve showed the typical rise and fall. Titres for OXK were negligible, and in only 1 patient was the titre for OX2 as high as for OX19. The authors were unable to decide which insect vector had been concerned in the transmission of infection. None of the patients was louse-infested, but all had been bitten by insects recently; fleas from rats found in the native huts, which were at one time used by a few of the men for a short period, and fleas from rats living in an ammunition dump, which had been guarded in turn by most of the patients, were possible vectors: *Xenopsylla cheopsis* and *X. braziliensis* were found in rats caught in the neighbourhood, and ticks infested almost every dog in the district. Lack of facilities prevented laboratory investigation to determine the insect vector and possible animal reservoir. The authors suggest that the results of the Weil-Felix tests resemble those which occur in the "OX19 group" of typhus cases in India.

569

VACCINATION AGAINST TYPHUS FEVER

by J. B. Penfold, *British Medical Journal*, 1, 114, 22/1/44

Agglutinins to *Proteus* OX19, OX2 and OXK suspensions are usually absent, or present in only low dilutions, in the blood serum of the normal English population. Felix (1944) has recorded the agglutinin titres for these suspensions in the blood serum of persons who had been inoculated with vaccines of typhus rickettsiae.

Dr. Penfold, a member of the Emergency Medical Service, has recorded similar findings in 23 persons who had been inoculated with a typhus vaccine prepared in Toronto from a louse-borne strain of *Rickettsia prowazeki* grown in the yolk-sac of chick embryos. Each person received 0.25 cm.³, 0.5 cm.³, and 1.0 cm.³ of vaccine subcutaneously at weekly intervals and 3 months later a fourth dose of 1.0 cm.³

Samples of blood were obtained for test (i) before the first injection, (ii) a fortnight after the third injection, (iii) before and (iv) a fortnight after the fourth injection. Sera were tested in dilutions from 1:5 to 1:640 with suspensions of *Proteus* OX19, OX2 and OXK. The tests were kept 4 hours at 56° C. and overnight at room-temperature before the results were read.

In the majority of cases there was an increase in the titre of agglutinins to all three suspensions after the first three injections. After the fourth injection the titres for OX19 and OX2 again rose, while the OXK titres were not appreciably altered. Even after the fourth injection, however, the highest titre for OX19 was 1:160 and for OX2, 1:80. If an increase of more than 100% in agglutinin titre for OX19 is regarded as significant, 14 of the 23 (61%) showed it after the first three injections and 17 (74%) after the fourth injection of the rickettsial vaccine. Reactions to the injections of vaccine were usually slight.

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¹ [see BMB 572]

570

NOTES ON TYPHUS FEVER IN THE MIDDLE EAST by W. Brockbank & S. R. F. Whittaker, *Lancet*, 1, 150-151, 29/1/44

The authors record clinical observations and laboratory findings in 10 sporadic cases of typhus fever admitted to a military hospital in the Middle East over a period of three months. All the patients were British soldiers and most of them had duties which brought them into close contact with civilian labour. Evidence of lice was found only in 1 case. Of the 10 cases, 8 were admitted to general wards where they remained until the rash appeared on the fifth or sixth day of illness. The authors comment on the difficulty of early diagnosis in the absence of an epidemic. In 2 cases, appearance of the rash was delayed until the 10th day and in these 2 the Weil-Felix test was of considerable help. In all cases the titre of agglutinins for OX19 was 1:120 or higher at some stage of the illness but, with the exception of the 2 cases in which the rash appeared late, the results were not significant until the clinical diagnosis was fairly certain. In 3 cases, the titre of agglutinins was higher for OX2 than for OX19, in 6 it was higher for OX19 than for OX2, while in 1 patient, who died on the 9th day of illness, the titre was the same (1:120) for both suspensions. In 6 cases specific rickettsial agglutination tests were made by Major van Rooyen at the Central Pathological Laboratory, Middle East Forces, and the diagnosis of louse-borne or epidemic typhus was confirmed. No case of cross-infection occurred, although several patients had been in general wards before delousing was carried out.

571

DRY BLOOD TEST FOR TYPHUS FEVER: Preliminary Report

by P. N. Bardhan, N. Tyagi & K. Boutros, *British Medical Journal*, 1, 253-254, 19/2/44

This preliminary report by medical officers of the Army Medical Corps from a field laboratory with the Middle East Force deals with a slide agglutination test; such tests have been used in the German Army on their Eastern Front where typhus fever has been a considerable risk during the war. The authors used a simple technique: two drops of blood obtained by pricking the ear or a finger were placed on a clean glass slide and allowed to dry. A drop of concentrated suspension of *Proteus* OX19 was placed on one blood drop and OX2 suspension on the other. The slide was allowed to stand for one minute and then the blood was mixed with the suspensions by rocking the slide. The slide was set aside but rocked occasionally; the results were read after 5-10 minutes with the naked eye and confirmed with the hand lens if necessary.

Blood specimens from 640 Egyptian labourers in various camps under military control were examined. Thirteen specimens gave positive results with OX19, and 2 of these

were positive to OX2 as well. These 13 were further examined by a complete Weil-Felix test in agglutination tubes. Of the 13 sera, 7 gave positive results with OX19 suspension, and 2 of these 7 agglutinated OX2 to a dilution of 1:50. These last 2 were from the same persons whose blood had given the positive results with OX2 on the slide. Weil-Felix tests were repeated at 4-7 day intervals on the 7 patients giving positive results. All of them gave a positive reaction to OX19 in serum dilutions of 1 in 250 or more in at least one of the tests. The history of these men showed that 3 were typhus cases, 2 were recently convalescent from typhus fever, while the remaining 2 could not be traced.

These observations suggested that, while all the typhus fever cases gave a positive slide test, a positive result with the slide test did not necessarily indicate a typhus infection. Thirty-three of the bloods which had given a negative slide test were tested by the full Weil-Felix technique; 25 of these were negative at 1:25 serum dilution, while none of the remaining 8 were positive in a serum dilution higher than 1:50 with either OX19 or OX2 suspension. The authors suggest that the slide test with dried blood might serve as a useful preliminary diagnostic method and that a complete Weil-Felix test need not be done unless the slide test is positive; they recommend that the slide method be tried out on a more extensive scale.

572

TECHNIQUE AND INTERPRETATION OF THE WEIL-FELIX TEST IN TYPHUS FEVER

by A. Felix, *Transactions of the Royal Society of Tropical Medicine and Hygiene*, 37, 321-341, March 1944

As suspensions of rickettsiae are not yet generally available for routine use in the diagnosis of the typhus group of fevers, the Weil-Felix reaction is likely to remain the standard test in many laboratories for some time. This article, written by one of the originators of the test at present working for the Emergency Public Health Laboratory Service, should prove helpful to pathologists required to assist in the diagnosis of suspected cases of typhus fever. The greater part of the paper is concerned with louse-borne typhus. Curves of agglutinin response to *Proteus* OX19 and OX2 in the sera of typhus patients studied in Poland and Turkey by the author during the last war are reproduced. The majority of cases of louse-borne typhus develop agglutinins for OX19 about the 4th or 5th day of illness, and the maximum titres reached are high. Moderately severe cases tend to show this type of response. In the most severe cases, however, a positive reaction tends to appear later, about the 6th or 7th day and the maximum titre reached is usually low (below 1:5000). The mildest cases may have either very low or high titres.

It is pointed out that, in sera from persons in countries free from typhus, agglutinins for *Proteus* OX19 and OX2 are only occasionally present, and then usually of titres below 1:100, which is frequently taken as the limit of normal agglutinins. In countries where typhus is endemic, agglutinins of much higher titre may be present in the sera of persons who have suffered from clinical or inapparent infection many months previously. Non-specific stimulation of OX agglutinins by other febrile infections (anamnestic rise) does not occur. Felix's experience agrees with that of Penfold (1944) in showing that OX19 agglutinins are produced irregularly, and only to low titre, following vaccination of healthy subjects with egg-yolk rickettsial vaccine; such agglutinins do not affect the diagnostic value of the Weil-Felix test, as a rising curve of OX agglutinins is diagnostic of typhus in the inoculated as well as in the uninoculated. Repeated tests on the serum are of especial importance in early diagnosis. When only the results of a single test are available, complete agglutination of a standard suspension in a serum dilution of 1:100 may be considered significant in an uninoculated person who is not a native of an endemic area. If the patient has been inoculated with rickettsial vaccine 2 or 3 months before his illness, complete agglutination at a titre of 1:200 or more may be regarded as strongly suggestive. Lower titres than these in the early stage of illness should not be ignored.

The author recommends keeping the tests at 37° C. for 2 hours and overnight at room-temperature before the final reading of results; the simple slide tests (see Bardhan,

Tyagi & Boutros, 1944) may be of value under the exceptional conditions which call for their use.

In murine typhus, agglutinins for OX19 generally appear in the patient's serum during the febrile period and have the same significance as in louse-borne typhus; these two varieties of the disease can be differentiated serologically only by tests with rickettsial suspensions (van Rooyen & Bearcroft, 1943; Stuart-Harris, Rettie & Oliver, 1943).

In the mild tick-borne typhus fever of the countries bordering the Mediterranean (*fièvre boutonneuse*), irregular results are obtained in agglutination tests with *Proteus* OX antigens. Significant reactions occur late in the disease and the titres are usually lower than in louse-borne typhus; agglutinins for OX2 are usually higher than for OX19. In tick-borne typhus in India, the types of agglutinin response to OX antigens have not yet been established. In scrub typhus or tsutsugamushi of the Far East, agglutinins for *Proteus* OXK only appear in the blood. The agglutination tests with this antigen are more liable to give false results owing to instability of the suspensions, which are more liable to agglutination with normal human serum. The significant titre of agglutinins is usually taken as 1:200. The agglutinins, however, rarely appear before the 2nd week and may not reach a maximum until the 3rd or 4th week from the onset of illness.

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¹ [see BMB 571]

² [see BMB 569]

³ [see BMB 567]

⁴ [see BMB 151]

573

NOTE ON THE PREPARATION OF SUSPENSIONS FOR THE WEIL-FELIX TEST

by R. F. Bridges, *Transactions of the Royal Society of Tropical Medicine and Hygiene*, 37, 343-344, March 1944

Lt.-Col. Bridges, of the Medical Research Council Standards Laboratory at Oxford, here gives details of the method used in the preparation of suspensions of the 3 *Proteus* OX strains that are employed in the Weil-Felix test. Cultures known to be suitable by preliminary tests with typhus serum are used. Roux bottles of agar are inoculated from 24-hour cultures in broth. After incubation of the Roux bottles for 24 hours, the growth is washed off with a small quantity of saline. The resulting suspension is filtered through cotton wool into screw-capped bottles and 4 volumes of 96% alcohol are added to 1 volume of suspension. The mixture is shaken thoroughly during the course of 1 hour; the supernatant alcohol is sucked off as far as possible and the remainder removed after centrifugation. The deposit of organisms is suspended in saline and shaken thoroughly to smooth out clumps; 2% buffered formol-saline (pH 7.6) is added to make the final concentration of formalin 0.25%. The suspension is standardized by the addition of further saline and buffered formol-saline, to a density equivalent to 4,500 million *Bact. coli* per ml. In the case of OXK suspension, the alcoholized organisms should be re-suspended in sterile distilled water in place of saline, and all further dilutions should be made with distilled water; the 2% formalin may be added in the form of buffered formol-saline as in the case of OX19 and OX2 strains.

574

TYPHUS FEVER IN GREAT BRITAIN

by A. P. Agnew & W. B. Kyles, *British Medical Journal*, 2, 10-11, 1/7/44

Although typhus fever has long since ceased to be endemic in Britain, the case recorded by Drs. Agnew and Kyles of the Emergency Medical Service in Scotland emphasizes the necessity of keeping this disease in mind in cases of unexplained pyrexia, especially among men who have recently returned from abroad.

The patient had embarked on December 20, 1943, from an area in which typhus fever was prevalent and on Decem-

ber 31, while still aboard ship, suffered from headache, cough and general muscular pains; his temperature was 102° F. [about 39° C.]. Bronchitis was diagnosed. From the sick-quarters on the ship he was admitted to hospital in Scotland on January 5, 1944. At this time the patient looked toxic and complained of severe headache, sore throat and cough. He had a rigor and collapsed before being put to bed, and on examination he was flushed and there were muco-pus in the nose and throat, definite bronchitis, slight general adenitis, and slight neck rigidity. His temperature was 103° F., pulse rate 80 and respirations 22 per minute. The patient's condition became slowly worse; on January 7, he was drowsy, restless and irritable; next day there was meningism, Cheyne-Stokes type of respiration and more definite evidence of bronchopneumonia. A Widal test was negative at this time. On January 9 a sparse macular rash, dusky red in colour, was present on the flanks and anterior aspects of the shoulders; the following day the Weil-Felix reaction was reported positive. After this date the patient slowly improved and by January 17, the temperature, pulse-rate and respirations were normal. The Weil-Felix test was repeated on January 15 and February 21. The highest titre of agglutinins in the patient's serum was recorded on January 15 when it was 1:12,800 for OX19; 1:400 for OX2; and 1:25 for OXK suspensions.

The decisive stages in reading a correct diagnosis were: (i) the recognition of typhus fever as a possible cause of the illness; (ii) the appearance of the rash; (iii) the positive Weil-Felix test. The authors consider that the patient acquired his infection before embarkation on December 20. The precautionary measures taken to prevent contact infection in the hospital are described. No secondary cases occurred and none of the other patients from the ship developed a positive Weil-Felix reaction.

Sources and Control of Hospital Infection

575

DUST AS VEHICLE OF INFECTION IN CHILDREN'S WARDS

by E. D. Hoare, J. R. O'Brien & A. G. Watkins, *Lancet*, 2, 666-667, 27/11/43

The pathogenicity of *Proteus morgani* has not been fully proven, and this report is not designed to bring evidence in this respect but rather to show the possible ways in which an organism of intestinal origin may spread throughout a ward. The paper comes from the Royal Infirmary, Cardiff, where Watkins is Physician in Children's Diseases. Hoare and O'Brien are on the staff of the Pathological Department of the Welsh National School of Medicine.

In a period of six months there were 14 infections with *Proteus morgani* in children in one ward, 10 of these appearing after admission. The infections were intestinal except in 1 case in which burns became infected. The infections could not be traced to the contamination of food during preparation or serving. Morgan's bacillus was, however, isolated from the air and the dust of the ward, from bed-linen, although not directly fouled by urine or faeces, and from flies. Experimentally, the organism was shown to survive 81 days on a blanket and up to 10 days in dust, and it could still be found on woollen garments after washing in soap and warm water. Sterilization of these garments or of blankets could be effected by exposing them for one hour to formaldehyde in a closed chamber.

576

HAEMOLYTIC STREPTOCOCCI IN THE DUST OF HOSPITAL WARDS, AND THEIR RELATIONSHIP TO INFECTION: A Report to the Medical Research Council

by D. G. ff. Edward, *Journal of Hygiene*, 43, 256-265, January 1944

The part played by dust in producing cross-infection has been the subject of increasing attention in recent years. This paper is a report to the Medical Research Council of

investigations on the dust in the wards of 2 contrasting types of hospital. The first investigation was made in the combined ear, nose, throat and eye ward (I) of an improvised Emergency Medical Service hospital. The second investigation was made in the children's ward (II) of another hospital. Ground-plans of these wards are reproduced in the original paper. In both cases, examinations of ward-dust were made weekly for a period of about 6 months.

The dust of ward I contained 300,000, and the dust of ward II 250,000, haemolytic streptococci per gram. Serological examination showed that about 33% of the streptococci isolated from the dust of ward I, and about 80% of those from ward II, were of group A. Examinations of swabs from throats and septic lesions of patients and staff showed that 27.8% of ward II patients were infected with haemolytic streptococci either on admission or at some time during their stay in hospital. The incidence of infection acquired in hospital was more than 12.2%. Typing of the organisms showed that the occurrence of a particular type in the dust often resulted from the presence of one or more infected persons in the ward. Conversely, it often happened that a particular type occurred in the dust before it was identified among inmates or staff of the ward. These strains may have been introduced to the ward by visitors.

There is as yet no definite evidence as to the significance of the presence of viable pathogenic bacteria in dust, and the investigations reported did not reveal a conclusive example of hospital cross-infection conveyed by dust. In the original paper the findings are reported in considerable detail.

577

SOME OBSERVATIONS ON HOSPITAL DUST WITH SPECIAL REFERENCE TO LIGHT AS A HYGIENIC SAFEGUARD

by L. P. Garrod, *British Medical Journal*, 1, 245-247, 19/2/44

The author, who is professor of bacteriology in the University of London and bacteriologist to St. Bartholomew's Hospital, studied the relation of dust to streptococcal cross-infections in hospital wards by determining the extent to which Group A haemolytic streptococci could be isolated from dust samples taken at different sites in the wards. It was readily shown that dust on the floors close to streptococcal cases and carriers had a high content of the organisms. Of samples from wards on the ground floor of the hospital, 72% yielded haemolytic streptococci, whereas only 18% of samples from the upper floor wards were positive. The lower floors were dark owing to the construction of brick walls in front of the windows, as a protection against bomb-blast, and it seemed probable that the comparatively low content of streptococci in the dust from the upper wards might be related to the free access of light.

Samples taken from different sites supported this view. Dust from, for example, well-lit window-ledges showed few haemolytic streptococci, while large numbers were usually isolated from darker situations. Streptococci in pus dried on slides survived longest in the refrigerator or a dark cupboard. They died much sooner in diffuse daylight and still more rapidly in a position exposed to sunlight, even though two layers of glass intervened.

Experiments were made with dust obtained with a vacuum-cleaner from floors known to be infected. In this dust haemolytic streptococci survived longer in the dark, and organisms of a type which had been responsible for an outbreak at the beginning of the trial were isolated from a sample kept in the dark for 195 days.

These results are further evidence that streptococcal epidemics at long intervals may be renewed by infected dust. Good natural illumination is a prime necessity for septic surgical cases. Daylight, even on a cloudy winter day in England, is lethal to bacteria, and ordinary glass is not an absolute bar to this effect.

578

THE CONTROL OF DUST-BORNE STREPTOCOCCAL INFECTION IN MEASLES WARDS

by J. Wright, R. Cruickshank & W. Gunn, *British Medical Journal*, 1, 611-614, 6/5/44

This is an account of a well-planned trial conducted by the clinical and bacteriological staff of one of the large infectious

diseases hospitals of London County Council. The haemolytic streptococcus is the chief secondary invader in measles and the main cause of its complications, especially otitis media, mastoiditis and bronchopneumonia. The object of the trial was to find out whether oil treatment of floors and bed-clothing would reduce the numbers of haemolytic streptococci in the air during sweeping and bed-making, and decrease the incidence of cross-infections and clinical complications due to haemolytic streptococci. Two identical measles wards were chosen for the test, and conditions in respect of admissions, bed-spacing and treatment were similar throughout the 12 weeks of the trial. In the test-ward, the floors were treated with crude paraffin oil every 4 weeks, and all blankets, sheets, towels and garments were treated with white oil by the technique described by Harwood, Powney & Edwards (1944). In the control ward no such measures were taken. Air-sampling was done with the slit-sampler of Bourdillon, Lidwell & Thomas (1941).

Preliminary investigations before the test period showed that conditions in the two wards were remarkably similar. During this period only the floor in the test-ward was oiled. In both, 36-39% of the patients were harbouring the type 6 streptococcus which, as the prevalent cross-infecting strain, was regarded as the "indicator" organism of the test; the cross-infection rate (i.e. the percentage of patients exposed to risk who acquired type 6 haemolytic streptococci) was 53-59% in each ward; the middle-ear complication rates due to this type were alike; this type prevailed in the air of both wards during bed-making.

During the test period, the mean bacterial count in the air during bed-making was 91% less, and the mean haemolytic streptococcus count was 98% less, in the treated than in the control ward. A similar difference during floor-sweeping was observed. The cross-infection rates due to type 6 haemolytic streptococci in the test and control wards were respectively 18.6% and 73.3%, and the middle-ear complication rates due to the same type were 2.8% and 14.3%.

The conclusion is that oiling of floors alone will not prevent dust-borne haemolytic streptococcal infection in measles wards, but that an effective degree of control is obtained when bed-clothes and linen are also treated.

The authors emphasize that the method must be further explored before it can be adopted for routine use. They also point out that measures other than those mentioned are necessary to prevent spread by direct contact by fingers, toys, etc., and by droplet spread from carriers amongst the staff and between new and convalescent patients.

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- ¹ [see BMB 579]

579

A NEW TECHNIQUE FOR THE APPLICATION OF DUST-LAYING OILS TO HOSPITAL BED-CLOTHES

by F. G. Harwood, J. Powney & C. W. Edwards, *British Medical Journal*, 1, 615-616, 6/5/44

The numbers of dust-borne bacteria in hospital wards can be greatly reduced by the application of 3% to 7% of liquid paraffin or "technical white oil" to the bedclothes (van den Ende, Edward & Lush, 1941; van den Ende & Thomas, 1941; Thomas & van den Ende, 1941). The authors, who are on the scientific staff of the British Launderers' Research Association, were faced with the problem of devising a means of impregnating the materials with an accurate quantity of oil. It was also necessary to find a method which could be readily used in hospital laundries and would ensure the complete removal of the oil from the liquor used for soaking the clothing, so that no recovery process for the unused oil would be needed.

These problems were solved by the use of a dilute oil-in-water emulsion stabilized with cetyl pyridinium bromide. For woollen materials a positively-charged emulsion stabilized by "Fixanol C" (a cation-active agent manufactured by Imperial Chemical Industries, Ltd.) was used. For cotton fabrics it was necessary to apply half the required amount of oil in this way, and to complete the process by a further treatment with the remainder of the oil stabilized by an

anion-active agent, "Teepol" (manufactured by *Technical Products, Ltd.*). The liquor should be slightly alkaline, pH 8. By these processes all the oil used was deposited on the fabrics.

The materials must be washed and rinsed, soft water being essential. The last rinsing water is adjusted to 100° F. [about 38° C.] and the stock solution containing 20 % of technical white oil and 2 % "Fixanol" is added in requisite amount. The rotating machine runs for 10 minutes, the goods are unloaded, hydro-extracted, and dried. Cotton articles receive 2 to 3 minutes in the same solution followed by 7 to 8 minutes in a similar emulsion stabilized with 3 % "Teepol".

The oil is not greatly removed by autoclaving, or by ordinary washing, and tends to accumulate with successive oilings. Since an oil content of more than 5 % to 7 % is undesirable, later treatments may have to be adjusted to minimize this accumulation.

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580

OILED FLOORS TO CONTROL RESPIRATORY INFECTION: An Army Experiment

by P. H. R. Anderson, J. A. Buchanan & J. J. MacPartland, *British Medical Journal*, 1, 616-617, 6/5/44

It has been shown by van den Ende, Lush & Edward (1940) and by Thomas (1941) that the number of dust-borne bacteria in the air of rooms can be diminished by treating the floors with crude paraffin oil. In order to determine whether the spread of air-borne infections could be decreased by this means, the authors, who are officers of the *Royal Army Medical Corps*, recorded over a period of 17 weeks during the winter the incidence of respiratory infections in two groups of soldiers who were living respectively in treated and untreated barracks. The units were large (1,300-1,700 men), and the soldiers in each group were similar in stage of training and living conditions. The buildings were practically identical. The medical officers agreed on a common standard for diagnosis of respiratory infection, the criteria being catarrh with obvious local signs, or a generalized infection accompanied by pyrexia.

While it is difficult to conduct a perfectly controlled experiment of this kind, the results suggest very strongly that the oiling of the floors was of value. The average weekly rate of respiratory infections in the treated unit was 7 per 1,000 men, against 38 in the control unit. An outbreak of almost epidemic proportions appeared only in the untreated unit at about the middle of the trial.

The oil, which is non-inflammable and has no unpleasant smell, is applied after thorough dry-sweeping of the floor. It dries in about 6 hours, leaving an imperceptible film. One gallon is needed to treat about 1,000 square feet [about 90 m.²] of floor-space. Subsequent applications may be made every four weeks. The oiled floor is easy to keep clean between treatments.

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581

A NOTE ON THE TRANSMISSIBILITY OF HAEMOLYTIC STREPTOCOCCAL INFECTION BY FLIES

by R. A. Shooter & P. M. Waterworth, *British Medical Journal*, 1, 247-248, 19/2/44

Working in a hospital of the British Emergency Medical Service, the authors attempted to find whether cross-infection in hospital wards was related to the carriage of haemolytic streptococci by flies. The observations were made in two surgical wards where there were cases of streptococcal infection, and a control series was made on flies caught in the laboratory. Of 27 flies caught in the wards, 9 gave cultures of haemolytic streptococci, 3 of which belonged to serological Group A. Coagulase-positive staphylococci were also iso-

lated. No haemolytic streptococci were isolated from the flies from the laboratory.

One of the Group A haemolytic streptococci was of type 4, a type which was responsible for a number of subsequent wound infections in this particular ward. The observations do not prove the transmission of haemolytic streptococci by flies, but suggest a possible explanation of spread of infection from case to case, or from one part of a hospital to another.

582

A SCHEME FOR THE PREVENTION OF CROSS INFECTION IN CHILDREN'S WARDS

by N. M. Jacoby, *Archives of Disease in Childhood*, 19, 26-28, March 1944

This short paper by the Registrar to the Children's Department of *Guy's Hospital* describes a new children's ward at the County Hospital, Pembury, and the precautions taken to prevent "cross-infection," i.e. infection conveyed to the child during its stay in hospital. The ward, which had accommodation for 35 children, consisted of 9 single rooms and 2 with two beds, 4 with four beds and 1 with six beds. A corridor ran the length of the ward and all but one room opened on to both the balcony and the corridor. Five of the single rooms were grouped together at one end behind swing doors, with separate bath, sluice and sterilizing rooms.

On admission each child was classified as to age and disease. The most careful isolation was given to the class most susceptible to cross-infection, i.e. infants under 18 months of age. Those with non-infectious ailments were placed in the segregated group of single rooms, and those with infections in the other single rooms. Only where infants had a similar infection to the other children, e.g. alimentary or respiratory, were they placed in a ward with others. The six-bedded room was reserved for children with tuberculosis, and children over 18 months with non-infectious diseases were grouped in the other rooms.

A high quality of nursing was considered essential to prevent spread of infection; a ratio of 5 patients to one nurse at night and 2 to one by day was desirable. Only senior nurses attended to the infants and each junior nurse had sole charge of certain older children. "Barrier nursing" was used for all infectious cases and the infants' food was prepared with full aseptic technique. Gauze masks were worn by everyone who entered the children's rooms, and few visitors were allowed.

Among the 268 children in the ward during one year 16 developed cross-infections, an incidence of 6%. The infections were evenly scattered through the year. Two were almost certainly contracted before admission and a third was due to neglect of the rules by a cleaner.

The author concludes that these figures compare favourably with others which have been published. Further improvement would probably follow the provision of more beds, so that when necessary children could be isolated on admission till the disease was classified, and so that children of different groups need never be put together. A more impermeable type of face mask is also thought to be desirable.

583

DESIGN OF DRESSING STATIONS AND CONTROL OF WOUND INFECTION

by W. Gissane, A. A. Miles & R. E. O. Williams, *British Journal of Industrial Medicine*, 1, 90-98, April 1944

The authors of this article, two of whom are members of a *Medical Research Council* Unit, are engaged on a study of the prevention and treatment of sepsis in industrial injuries, at the Birmingham Accident Hospital. It is their thesis that many injuries, instead of being protected from infection from the time they come under medical care, become infected during treatment and that such infection can be greatly reduced by the adoption of a simple aseptic routine in treatment. The source of infection may be the nose, throat or skin of the patient or his attendant, or organisms may be carried from other infected wounds on the hands or instruments of the dresser. In addition to obviously septic wounds, many which appear "clean" may harbour *Strept. pyogenes* or *Staph. aureus*, and so be a potential source of infection. This article sets out some ways in which the infection of

wounds can be minimized in a busy dressing station in hospital or factory.

The chief vehicles of infection are (a) hands and pocket-scissors of the dressers, (b) instruments, (c) dressings packed in bulk and contaminated by hands or instruments when some are removed. To ensure that hands are washed and instruments sterilized after every dressing, the wash-basin and sterilizer should be within easy reach. For a dresser working alone, dressings can be packed separately or collected in a bowl before each dressing is started; but if assistance is available, one nurse should act as "server" and hand out clean instruments and dressings. The bin for dirty dressings should be close to the patient and capacious enough to be used for several hours without emptying.

The ideal routine is: (i) setting out instruments, dressings, etc. on the trolley; (ii) removal of soiled dressings; (iii) inspection and treatment of the wound; (iv) re-dressing the wound; (v) cleaning and sterilizing instruments and bowls; (vi) washing hands; (vii) recording the treatment.

Adherence to this routine does not involve more complicated procedures; on the contrary, work is often simplified thereby. Failure to adhere to it is often due to inconvenience in the arrangement of the dressing station. Plans of well- and badly-arranged rooms are shown in the article, to illustrate the great saving of labour which may follow a careful arrangement. The most important points in arrangement are:

1. The dresser should have to walk only a few steps between patient, trolley, sterilizer, wash-basin and records desk.
2. The paths taken by the dresser and patient should not cross.
3. Good lighting, either natural or artificial, should be provided. For the latter, fluorescent tubular lamps are the best.
4. Where a doctor's desk and chair are provided, a wash-basin should be close to the chair.

584

CONTROL OF STAPHYLOCOCCUS AUREUS INFECTIONS IN A MATERNITY DEPARTMENT

by F. A. Knott & J. B. Blaikley, *Journal of Obstetrics and Gynaecology of the British Empire*, 51, 386-400, October 1944

This interesting paper by the Director of the Bacteriological Department, and an Assistant Obstetric Surgeon, Guy's Hospital, describes the course of several incompletely controlled epidemics of staphylococcal infection in a maternity department, and the measures which were later effectively imposed to prevent such outbreaks. Between March 1942 and February 1943 five epidemics occurred, two of which necessitated closing the ward. At the end of this time a new régime was introduced, the object of which was, without adding excessively to the labour of the staff, (a) to exclude carriers of pathogenic staphylococci, and (b) to prevent carriage of organisms from one individual to another. In the following year, with the new routine established, no epidemics occurred and, as a result, it was possible to admit 30% more patients. The maternity department is a self-contained unit consisting of a ward of 24 beds, with separate nursery and isolation wards and its own theatre, kitchen, dairy, etc.

Bacteriological methods: For taking samples from unopened abscesses or bullae aseptic puncture was performed: discharging lesions were first cleaned of superficial material. Nose, pharynx, eyes and vagina were cultured by swab in the usual way. The skin was examined by rubbing with a moist swab or square of gauze which was put into broth and incubated for 5 hours, after which blood-agar plates were inoculated. Dust samples from, e.g. floor and utensils, were taken in a similar way.

Two or three strains of staphylococci were isolated from each primary culture and examined separately. The strains were classed in 4 "grades" according to their cultural and biochemical reactions. Some were also typed by Cowan's technique, but the speed and simplicity of grading by cultural reactions recommended it for routine purposes, and in practice epidemics could be controlled on this basis. Grade A and B strains were considered to be invasive, and patients or carriers with these strains were excluded from the ward. Of 142 strains from infective lesions, 115 fell into grades A and B, while only 5 out of 50 from "normal" skin did so.

GRADING OF STAPHYLOCOCCI BY CULTURAL REACTIONS

	Grade A	Grade B	Grade C	Grade D
Pigment	+++	++	+	+
Coagulase	+++	++	±	±
Haemolysin	+++	+	±	±
Gelatin	+	±	±	—
Mannite	A(24)	A(48)	A(72)	A(72 or ∞)
Lactose	A(24)	A(24)	A(48)	A(72)
Saccharose	A(24)	A(24)	A(48)	A(72)
Maltose	A(24)	A(24)	A(38)	A(48 or 72)
Glucose	A(24)	A(24)	A(24)	A(24 or 48)

A = production of acid; numerals represent time in hours at which reaction appeared

History of the epidemics: All the epidemics started suddenly and subsided gradually in 2 or 3 weeks. In the mothers there was inflammation of the breast, with or without supuration, or genital infection with slight fever, and in the babies nasal discharge, conjunctivitis or skin lesions varying in severity from septic spots to pemphigus.

In the first outbreak, a grade-A staphylococcus was found in cultures from the nose, throat or hand of 7 nurses and 7 dressers, and from dusting-powder, olive oil and towels used for the babies. The epidemic probably arose from a towel in the maternity-department kitchen which, in breach of the rules, was used by nurses from an adjacent ward containing septic surgical cases.

Soon after a short ward-closure another epidemic broke out. The need for the strict exclusion of carriers had not at this time been realized, and 5 of the previous carriers who had returned to duty were found still to be carrying a grade-A staphylococcus. Three further epidemics were due respectively to a nurse with recurrent colds and hay fever, a patient with a head cold, and a nurse carrying grade-B staphylococci in the nose and on the hands.

After this it was realized that intermittent or incomplete prophylaxis would not abolish epidemics, and that a stricter régime was required.

Prophylactic régime: This was based on the facts which had been revealed by investigation of the epidemics:

- i. The infection was usually introduced by carriers.
- ii. As masks were systematically worn, direct infection from the skin, and especially the hands, of carriers was probably an important factor.
- iii. Feeding-bottles and other ward equipment became more heavily infected than floor-dust.

The following routine was established:

1. Cultures were made from the nose, throat and hands of all nurses before starting work in the department. If a grade-A or -B staphylococcus was found, the nurse was excluded until it had disappeared.

2. Similar cultures were made every fortnight, and at the beginning of a cold, from nurses working in the department. *Staph. aureus* in the primary culture excluded the nurse until it had been graded; if it was of grade C or D she was re-admitted.

3. Similar cultures were made from all new patients and in addition from the vagina and from any inflammatory lesion. The patient was not allowed into the main ward until the primary cultures had been examined and until *Staph. aureus*, if present, had been graded.

4. Masks were worn during attention to patients and babies, and always in the nursery.

5. Before and after attending to patients and babies the hands and forearms were held under a strong spray of water regulated by a foot or elbow tap and dried on a sterile towel which was immediately discarded.

6. Babies were protected from contact with staphylococci, and from the slight injuries to the skin which may form a site of entry, by handling them as little as possible. They were bathed only at birth, at the separation of the umbilical cord and thereafter at intervals of 5 or 6 days.

7. Baths and bathing equipment were thoroughly washed after use.

8. Olive oil, dusting powder, etc., for the babies' use were sterilized daily.

9. Patients and babies with any *Staph. aureus* grade-A or -B infection were isolated.

10. Babies were removed from the ward during visiting hours and visitors were not encouraged. Fathers, if they

wore a mask, might see the babies but were not allowed to handle them.

Results of the new régime: The report covers a period of 14 months after the institution of the new regulations. The most striking effect is set out in a table which shows that, though there were almost always from 1 to 5 cases isolated from the ward because of infection, and some nurses excluded because they were carriers of grade-A or -B staphylococci, yet no epidemic developed during that period. The incidence of infection expressed as a percentage of confinements fell from 43 to 7.7, with an increased proportion of trivial infections. The grading of staphylococci which had been adopted appeared to be justified, as at all times there was an average of 5 carriers of grade-C and -D staphylococci among the staff and these were allowed to remain on duty.

The authors discuss also some tentative deductions made from their investigations. Briefly they suggest (i) that infection of dust and utensils by virulent staphylococci follows rather than precedes an epidemic; (ii) that staphylococci implanted on an infant's skin gradually spread, and that spread is most rapid on moist areas and in flexures; invasion is often determined by a slight injury or area of lowered resistance; (iii) staphylococci are transferred from an infected infant to the hands and nipple of the mother, from where they spread over the body. Inflammation of the breast may follow and the same grade of staphylococcus be recovered from the milk. *Staph. aureus* is often present in milk from a "normal" breast, but in this case it is almost always of grade C or D. No instance of primary infection from the milk was seen.

[see also BMB 31: a review of a report (*J. Hyg., Camb.* 1942, 42, 474) to the Medical Research Council by J. T. Duncan & J. Walker on *Staphylococcus aureus* in the milk of nursing mothers and the alimentary canal of their infants.]

REFERENCE

Cowan, S. T. (1939) *J. Path. Bact.* 48, 169

Aerial Disinfection*

585

THE USE OF ANTISEPTIC SPRAYS FOR AIR STERILIZATION: A Summary of a Report to the Medical Research Council

by R. J. V. Pulvertaft, *Journal of Hygiene*, 43, 352-356, April 1944

This is a summary of a report to the *Medical Research Council*. Colonel Pulvertaft, at present serving in the Royal Army Medical Corps, is a Reader in Pathology of the University of London.

The plan of the experiments now described was to create a fine mist of bacteria for 2 minutes in a room of 850 cubic feet [about 240 m.³] capacity by means of an "Atmozon" nebulizer operated by a mechanically driven compressor, and to count the number of viable bacteria which settled on plates of culture medium during 5-minute periods afterwards. The results were compared with those obtained in similar experiments in which the room had been sprayed for 5 minutes immediately before infection with a mist of antiseptic also produced by a nebulizer. An output of 1 ml. of antiseptic per minute was generally used. The test organism mainly employed was a haemolytic streptococcus of serological group C, sprayed from a diluted culture in serum broth.

Of the antiseptics shown to be effective, the following are mentioned:

i. *Eugenol carbinol* is rapid in action and effective in low concentration in propylene glycol. It is easily procurable, but it deteriorates rapidly in solution and is slightly irritating to the nose and eyes.

ii. *Sodium hypochlorite* is inexpensive, non-toxic, highly effective at low concentrations (5 ml. of a 1% solution in the air of a room of 1,000 cubic feet [about 280 m.³]) and has a deodorant action. The nebulizer must be resistant to its

corrosive effect and must not emit large drops of spray which may damage coloured fabrics.

iii. *Hexyl resorcinol* in propylene glycol is effective but slower than the two antiseptics previously mentioned.

iv. *Catechol* is non-irritant and strongly bactericidal in 2.5% solution in propylene glycol. It is, however, relatively toxic and is likely to prove more useful for horticultural and industrial purposes than for human habitations.

Antiseptic mists were not effective against organisms dried *in vacuo* or shaken into the air from a blanket on which they had been dried. This may be due to their occurrence in clumps and in association with comparatively large dust-particles.

As a solvent, glycerine has the disadvantage of reducing the output of mist, and it cannot be used with hypochlorites owing to the formation of chloroform. Propylene glycol which also cannot be used with hypochlorites is an effective solvent and has itself an antiseptic action.

Antiseptic mists may have a cumulative action, so that an effective concentration may be maintained by the subsequent atomization of smaller amounts of antiseptic. The addition of various surface-tension-reducing agents did not enhance the action of the mists.

Experiments were made to find whether animals which breathed antiseptics in the form of mist or fine powder developed resistance to infection by inhalation. Hypochlorites, hexyl resorcinol, acriflavine, proflavine and sulphathiazole were tried. This treatment had no effect on the incidence or severity of inhalation infection with *Pasteurella muriseptica*.

In conclusion, the author states that a good antiseptic for atomization should bring about 90% reduction in bacteria with an air concentration of 1 g. in 20,000 cubic feet [about 5,660 m.³]. In the absence of epidemic respiratory disease even crowded rooms contain few organisms from the respiratory tract, and mists in the concentrations used are unlikely to be of value except in time of epidemic disease. Practical points to be considered are: the avoidance of an over-concentrated solution, which may be irritant, or an over-diluted one, which, in reaching effective concentration, may unduly increase humidity; the advantage of several small nebulizers over a single large one, and of continuous or semi-continuous mechanical operation. The author agrees with Baker, Finn & Twort (1940) that sodium hypochlorite seems the most suitable antiseptic for general use under present conditions.

REFERENCE

Baker, A. H., Finn, S. R. & Twort, C. C. (1940) *J. Hyg., Camb.* 40, 560

586

GERMICIDAL MISTS AND VAPOURS IN AIR DISINFECTION

by A. H. Baker & C. C. Twort, *Journal of Hygiene*, 43, 382-394, September 1944

This is the latest of a series of papers on air disinfection by the scientific staff of the Portslade Research Laboratories, Sussex, England. As the air of rooms and public places is in practice constantly subject to re-infection, an effective disinfecting agent must possess the qualities of persistence, stability and durability. Persistence implies that some at least of the constituents of a mist remain in the particulate state for a given time. Stability implies that the composition of the particles does not change, though their size may alter. Durability refers to active life as a germicide. The authors' researches were mainly carried out in an experimental chamber, 3.03 m.³ in capacity, in which the antiseptic mists and bacteria could be nebulized and plates of culture medium exposed. In the experiments now described, the properties of a number of higher phenols were investigated, particularly in relation to the possibility of obtaining a lasting action. The bacterial mist chiefly used consisted of a strain of *C. xerosis* suspended in broth or saliva. Striking differences were observed in the sensitivity of the phenols according to the agent in which the test organism was emulsified.

The following heat-volatilized germicides were tested: resorcinol, hydroquinone, pyrogallol, pentachlorophenol, benzyl cresol, benzyl phenol, hexyl resorcinol, eugenol

* [see also BMB 557]

ANAEROBIC INFECTIONS OF WAR WOUNDS IN THE MIDDLE EAST

by J. D. MacLennan, *Lancet*, 2, 63-66, 94-99 & 123-126, 17/7/43, 24/7/43 & 31/7/43

The author of this paper, which is based on an investigation carried out under the direction of the Deputy Director of Pathology, Middle East Forces, went to the Middle East with a special knowledge of anaerobic bacteria, and has been able to make a comprehensive study of anaerobic wound infections which is the first of its kind in the English medical literature since the war of 1914-18. His three papers contain much detailed information and observations both of theoretical interest and of great practical value. His survey embraces the whole of the wounded in the Middle East Forces from the beginning of the war until the second battle of El Alamein, a period in which there were six distinct campaigns.

He first points out that the term anaerobic infection includes several different conditions. Tetanus is deliberately excluded, since observations made on this disease have already been published (Boyd & MacLennan, 1942). Fusospirochaetal infection and the type of spreading gangrene of the skin due to an anaerobic streptococcus and described by Meleney were rarely encountered. Extensive infection of muscle simulating true gas gangrene and caused by an anaerobic streptococcus, always accompanied by some other aerobic organism, is described more fully; 19 such cases were seen. The remaining conditions are due to clostridia of the gas gangrene group, and are divided into 3 categories. Simple contamination of wounds by such bacteria, with some multiplication but no tissue invasion, was seen in 20-30% of all wounded. In about 5% of such cases anaerobic cellulitis developed; this is an infection of connective tissue which produces gas and may be extensive, but is unaccompanied by serious systemic disturbance. The third condition is clostridial myositis, or true gas gangrene, a rapidly spreading infection of living muscle, having an acute and usually early onset, and causing pain, swelling and severe constitutional disturbance. This occurred in about 1.5% of wounds containing anaerobes and 0.4% of all wounds.

Of 164 known cases of gas gangrene, there were 146 in which the author fully analysed the anaerobic flora, and the frequency with which each of many species was found, either alone or in combination with others, is set out in detail, together with an account of the clinical features characteristic of each. *Cl. welchii* was the most frequent, although it did not preponderate over all others as it did among wounded in France in the last war. It causes the classical condition with early onset and abundant gas production. *Cl. oedematiens* came next in frequency; the incubation period is longer, oedema is produced rather than gas, the foul smell may be absent, and a "sense of weight" in the limb is a marked feature. Other clostridia found alone in smaller numbers of cases were *Cl. septicum*, *Cl. histolyticum* (all 10 cases in which this organism occurred, once alone and 9 times in combination with others, were fatal), *Cl. bifermentans* and *Cl. fallax*. The mortality of mixed infections was higher than in those due to a single clostridium, and the possibility of synergic action between them is discussed.

Treatment is fully described. The prophylactic use of sulphonamides and reliance on them alone in treatment were disappointing, but adequate combined antitoxin and sulphonamide treatment appears to have been successful. A study was also made of the flora of desert sand collected at many different points between Benghazi and Egypt, from which it seems that the source of infection must be sought elsewhere. Pathogenic clostridia could much more frequently be cultivated from soldiers' uniforms, and the author regards this as the probable source of infection, and faecal contamination as the cause of its infectivity.

REFERENCE

- 1 Boyd, J. S. K., & MacLennan, J. D. (1942) *Lancet*, 2, 745

1 [see BMB 81]

BACTERIOLOGY OF WAR WOUNDS

by R. J. V. Pulvertaft, *Lancet*, 2, 1-2, 3/7/43

This short paper embodies the conclusions of an experienced bacteriologist after two years' study of infection in war wounds. The author who, before the war, was on the staff of the Westminster Hospital, London, held the position of Deputy Assistant Director of Pathology and Officer Commanding the Central Pathological Laboratory of the Middle East Forces.

He begins by insisting on the need for using a standard method of taking material for investigation in any systematic study of wound infection. Samples taken by different methods or inoculated on to different media show widely different results. Again, samples taken from the depth and the surface of a wound differ quantitatively, though generally not qualitatively. In this investigation swabs taken by the surgeon were moistened in the laboratory and then inoculated on to blood-agar plates, the surface of which had been dried with alcohol (to prevent the spread of *Proteus* and *Ps. pyocyanea*). Anaerobic cultures were also made and these were later subcultured aerobically on to blood-agar plates.

The wounds studied are divided into two groups—head wounds and wounds elsewhere. The distribution of the various species of bacteria is similar in the two groups except that *Staph. aureus* (haemolytic and non-haemolytic) was present in 75.5% of 140 head wounds and only 54% of other wounds. In agreement with other investigators the author found that the bacterial flora of a wound might alter considerably at successive samplings. The change frequently synchronized with a change of treatment, and the introduction of certain types of antiseptic for dressing the wounds was almost invariably followed by the appearance of certain species of bacteria. For these reasons the author inclines to attribute the appearance of fresh species to organisms "latent" in the wound and not, in most cases, to infection from outside.

The author goes on to point out that while in this war deaths attributable to sepsis alone are very few (for instance 5 out of 2,472 battle casualties at a military hospital in the Middle East), in the last year of the war of 1914-1918 they were probably no more (for instance a death rate of 0.5% from all causes including gas gangrene is quoted in the Official Medical History of the War). A more important question is whether, by the introduction of sulphonamides and the closed-plaster treatment, the incidence of prolonged sepsis has been reduced. Many patients are still seen who, months after wounding, have suppurating wounds, with fever, intractable anaemia and nephritis. The author favours an attempt to reduce the numbers of these patients by relying less on the closed-plaster method and more on the attempt to eliminate bacteria from the wound by persistent local treatment. [At the time this paper was published the first systematic trial of penicillin in war wounds had only just begun.]

WOUND INFECTION: A PRELIMINARY NOTE ON A COMBINED CLINICAL AND BACTERIOLOGICAL INVESTIGATION OF 708 WOUNDS

by H. L. de Waal, *Edinburgh Medical Journal*, 50, 577-588, October 1943

The author, who is a Lecturer in Bacteriology in the University of Edinburgh, carried out this investigation in the departments of Surgery and Bacteriology of that University. His object was to follow the bacteriology of wounds and burns from admission to hospital until healing was complete and to correlate it with treatment and clinical progress. The many possible sources of infection of wounds in hospital—air, blankets, throats of patients and attendants and so on—were also investigated bacteriologically. As he points out, 708 cases is a small number where so many variables are concerned and "it is doubtful whether anything short of several thousand would be of real statistical value." He presents here his principal findings and deductions, pending a more complete analysis of the data.

Methods: The swabs were usually taken by the bacteriologist himself. Wounds were sampled just before operation, at each dressing for the next week, and thereafter every 2 to 5 days. Estimates of the numbers of bacteria present

were made chiefly from films. Wounds under plaster were sampled by absorbent threads which were laid on the wound surface and passed across the skin between layers of vaseline gauze; the gauze passed through a vulcanite funnel in the plaster 2 cm. from the edge of the wound, thus bringing the thread to the surface. Throat-swabs were taken periodically from the patients under investigation and, when indicated, from all the staff and patients in a ward.

Results: The bacteriology of the wounds at the time of admission to hospital supported the view now often put forward (e.g. Gissane, Miles & Williams, 1944) that wounds may become infected during treatment if this is not efficiently carried out. The number of wounds contaminated by bacteria increased with increasing delay before admission. Those which had been "cleaned" before admission carried more bacteria of all types than those which had simply been dressed, and twice as many were infected with streptococci. A sterile covering put on soon after injury was the most favourable first-aid treatment. Haemolytic streptococci were more frequent in wounds of the head, neck and upper limb, and coliform bacilli, *Proteus*, *B. pyocyaneus* and clostridia in wounds of the groin, perineum and thigh.

After admission to hospital 86% of all wounds and 67% of burns became infected, the majority with organisms of low pathogenicity; 146 cases acquired a haemolytic streptococcus and 231 *Staph. pyogenes*. On many occasions, from the time the patient arrives in hospital, the wound is uncovered and exposed to potential infection. Among possible sources are the nose and throat of patients and attendants (masks are often inefficient), the skin near the wound, dust from bed-clothes if the patient moves during the dressing, slipped bandages and baths. Of 38 wounds treated in closed plaster, 34 became infected, mainly with non-pathogenic staphylococci and *Proteus*.

Treatment: The author emphasizes that the value of the different antiseptics used locally is difficult to assess because of the large number of variable factors. He gives no indication of the principles on which the wounds and burns were selected for the various treatments. The local applications used were acriflavine 0.1%, gentian violet 1.0%, sulphanilamide, sulphapyridine, albucid 2.5% to 30%, tannic acid and penicillin. The author concluded that penicillin was the most promising of all, but as it was used in only a few cases the results were excluded. Of the rest, acriflavine appeared to be the most satisfactory, as it acted on all kinds of bacteria and was not inhibited by pus. As it tended to delay healing it was best used for 4-5 days and then replaced by another antiseptic, preferably a sulphonamide.

The figures given show that the three sulphonamides all reduced infection by streptococci, but by no other organism. The treatment of burns with tannic acid reduced infection by bacteria of all types, and the author recommends this method for parts where there is little movement, pressure or liability to wetting. For the flexures, sulphonamides in paste or paraffined gauze were satisfactory. The importance of surgical excision of wounds as a means of reducing infection is emphasized.

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¹ [see *BMB* 583]

592

EARLY DIAGNOSIS OF WOUND INFECTION WITH SPECIAL REFERENCE TO MIXED INFECTIONS

by D. McClean & H. J. Rogers, *Lancet*, 1, 707-708, 5/6/43

This paper by two workers from the *Lister* Institute, Elstree, is a supplementary note on work previously reported by McClean, Rogers & Williams (1943). The earlier paper described experimental work which suggested that the infection of wounds by organisms of the gas-gangrene group might be detected at an early stage before it could be recognized by clinical or ordinary bacteriological examination. The methods advocated depend upon the rapid detection of enzymes produced by bacteria proliferating in the wound. Detailed descriptions of the technique used in these tests were given.

In the present paper, the authors describe the influence of mixed infections by staphylococci or streptococci together with organisms of the gas-gangrene group on the character

of the resulting infection, and recommend certain modifications in the tests previously described in order that the nature of the bacterial source of the enzymes may be determined.

It was found that the addition of hyaluronidase-producing staphylococci or streptococci to an infection by non-hyaluronidase-producing *Cl. welchii* or *oedematiens* profoundly modifies the character of the infection. The extension of the infected area is more rapid and, in the case of *welchii* infections, the character of the exudate is altered; it becomes more fluid. Both the staphylococci and the streptococci are found in the exudate in numbers approximately equal to those of the accompanying anaerobe. This is in striking contrast to the failure of either the staphylococci or streptococci alone to initiate a generalized infection. Staphylococcal or streptococcal hyaluronidase is present in high titre in both the muscle extracts and the exudates.

Further observations showed that if a hyaluronidase-producing aerobe accompanies a hyaluronidase-producing member of the gas-gangrene group, then not only will both organisms be found in the tissues, but hyaluronidase from both bacterial species will be present. This will complicate the diagnosis of the bacterial source of the hyaluronidase found in the wound exudate. For this reason, the authors recommend that polyvalent anti-sera should be used in neutralization tests in place of the monovalent sera previously described. Particulars are given of the composition of these polyvalent diagnostic sera.

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¹ [see *BMB* 80]

593

HYALURONIDASE PRODUCTION BY HAEMOLYTIC STREPTOCOCCI OF HUMAN ORIGIN

by N. Crowley, *Journal of Pathology and Bacteriology*, 56, 27-35, January 1944

An enzyme, hyaluronidase, has recently been recognized which has the capacity to hydrolyse the mucin-like polysaccharide hyaluronic acid (Chain & Duthie, 1940). This enzyme is almost certainly identical with the "spreading factor" found in certain tissues and produced by some bacteria, particularly staphylococci, streptococci and the gas-gangrene organisms (Duran-Reynals, 1933; McClean, 1936). As hyaluronidase has the capacity to lyse the capsules of streptococci, it appears unlikely that the same strain of streptococcus would produce both hyaluronidase and a capsule. As previous work on this point was conflicting, the present author, working in the Emergency Public Health Laboratory, Cambridge, examined 376 strains of streptococci of known group and type for both hyaluronidase-production and capsule-formation.

Technical methods: For capsule-formation, cultures which had been grown overnight in 20% rabbit-serum broth were inoculated heavily into the same medium, and after 2 hours' incubation the centrifuged deposit was examined for capsules by the india-ink method of Butt, Bonyng & Joyce (1936). In some strains the appearance of the colonies on freshly poured neo-peptone blood-agar plates (Dawson, Hobby & Olmstead, 1938) was also studied.

Hyaluronidase-production was tested by McClean's method (McClean, Rogers & Williams, 1943; McClean, 1943). This depends on the fact that a mixture of horse serum and potassium hyaluronate can be clotted by acetic acid, but that clotting is prevented by hyaluronidase. In these experiments the substrate was composed of equal parts of an 0.2% aqueous solution of potassium hyaluronate (prepared from human umbilical cord) and of horse serum diluted 1 in 3 with distilled water. The streptococci were grown for 18 hours in veal tryptic digest broth enriched with 0.1% glucose. The culture was centrifuged and the supernatant fluid was tested at a dilution of 1:10 and, if positive, re-tested at tenfold serial dilutions. If only the lowest dilution was positive, a further test at a dilution of 1:2 was carried out.

Results: A decisive answer to the question posed was obtained in that, of 122 strains which produced hyaluronidase, none showed a capsule, whereas of 264 strains not producing hyaluronidase 186 were encapsulated. In group A

(Lancefield), 308 strains were examined. Although 14 or more strains were examined in each of types 1, 2, 3, 4, 8, 11, 12, 22, 25 and 27 (the remainder being distributed in smaller numbers among 18 other types), in only 2 types were hyaluronidase-producers found—41 out of 47 in type 4, and 23 out of 24 in type 22. In group C, all strains were non-capsulated and 35 out of 55 produced hyaluronidase. In group G all (13) were non-capsulated and all produced hyaluronidase.

The strains tested had been isolated from a wide variety of streptococcal infections or from normal carriers (in a few types only, stock cultures were tested). The author concluded that "there was little correlation between the power to produce hyaluronidase and the virulence of the strain for human beings". Where strains of the same type of streptococcus were isolated from several individuals in close contact (e.g. in an epidemic of scarlet fever) the characteristics, as regards hyaluronidase-production and capsule-formation, were the same in all.

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¹ McClean, D., Rogers, H. J. & Williams, B. W. (1943) *Lancet*, 1, 355

¹ [see BMB 80]

594

HYALURONIDASES IN INFECTED WOUNDS

by J. D. MacLennan, *Lancet*, 2, 433-434, 30/9/44

Hyaluronidase is produced by various species of pathogenic bacteria, including *Strept. pyogenes*, *Staph. pyogenes*, *Strept. pneumoniae* and some of the clostridia (Duran-Reynals, 1933; McClean, 1936; 1941). It can be detected in infected tissues and in inflammatory exudates. The hyaluronidase produced by each organism can be used to prepare an antiserum which is apparently specific for the species of origin. Hyaluronidase can be detected by the mucin-clot-prevention test of McClean and his collaborators (McClean, 1943; McClean, Rogers & Williams, 1943; McClean & Rogers, 1943), and they have suggested that this test carried out on tissues or exudates, combined with neutralization by specific antisera, might form a rapid method of identifying the organism in clinical infections. In this paper Major J. D. MacLennan of the Royal Army Medical Corps reports the results of carrying out this test on material from 51 battle casualties with infected or contaminated wounds, including 12 cases of gas gangrene. The samples of muscle or exudate were taken at operation and tested as soon as possible, usually within an hour.

The organisms present in the wounds included *Cl. welchii*, *oedematiens* and *septicum*, *Strept. pyogenes*, *Staph. pyogenes* and anaerobic streptococci. Six samples gave a partial or slight positive result, i.e. partial destruction of the clot or prevention of clotting at a dilution of 1/1 or 1/2. Only one was definitely positive, preventing clotting at 1/128 and being neutralized by the appropriate antiserum; this sample consisted of pus from an empyema infected with *Strept. pyogenes*.

The author was at a loss to explain the large proportion of negative results—44 out of 51. Two of the strains of *Cl. welchii* which had given negative results in man were tested in animals and gave strongly positive results 12 hours after injection. He points out that the one decisively positive clinical test came from the only case infected by a single organism.

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¹ [see BMB 592]

² [see BMB 80]

595

DETECTION OF BACTERIAL ENZYMES IN INFECTED TISSUES

by D. McClean & H. J. Rogers, *Lancet*, 2, 434-436, 30/9/44

Work reported by McLennan (1944) showed that the mucin-clot-prevention test for hyaluronidase was negative in infections in man caused by organisms known to produce this enzyme. In the present work Drs. McClean and Rogers, of the Lister Institute of Preventive Medicine, investigated experimentally the reasons for this unexpected result. Hyaluronidase and lecithinase were estimated in muscle extracts and oedema fluid of experimental animals by the methods already described (McClean, Rogers & Williams, 1943; McClean, 1943).

Twelve guinea-pigs were injected intramuscularly with washed 18-hour cultures of *Cl. welchii* to which CaCl_2 had been added. Four were injected with 200 units of monovalent *Cl. welchii* antitoxic serum at 2 hours after infection and 4 at 4 hours after infection. The remaining 4 were not treated and were used as controls. Two of each group were killed 6 hours after infection and the rest at 22 hours. This experiment was performed four times with consistent results. The highest dilution at which muscle extracts and oedema fluid of control animals gave a positive result varied between 1:16 and 1:3848. In 3 out of the 4 experiments, the tests showed decisively that antitoxic serum greatly inhibited or completely suppressed hyaluronidase production. In the 4th there was slight inhibition. Lecithinase production also was inhibited or suppressed by the antitoxin in all experiments.

Reviewing Major MacLennan's 12 cases of gas gangrene the authors point out that several of the negative results can be accounted for either by the administration of antitoxic serum or by the fact that the infecting organism was *Cl. oedematiens*, of which type B produces little and type A no hyaluronidase. But in at least 1 case where *Cl. welchii* was the organism responsible for the infection and no antitoxin had been given the test was negative. It appears that other factors besides the administration of antitoxin modify the results in man. Further animal experiments showed that neither the size of the initial infecting dose of *Cl. welchii* nor the presence of a proteolytic organism such as *Cl. histolyticum* affected the result in animals.

In another series of experiments a streptococcus which did not produce hyaluronidase, *Cl. histolyticum*, and a preparation of hyaluronidase were injected into guinea-pigs separately and in combination. The streptococcus both with and without hyaluronidase was harmless, but when added alone to *Cl. histolyticum* it hastened death, and this effect was increased if hyaluronidase was injected in addition.

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³ McLennan, J. D. (1944) *Lancet*, 2, 433

¹ [see BMB 592]

² [see BMB 80]

³ [see BMB 594]

596

INFECTION OF CAT-BITE AND DOG-BITE WOUNDS WITH PASTEURILLA SEPTICA

by E. N. Allott, R. Cruickshank, R. Cyrlas-Williams, V. Glass, I. H. Meyer, E. Straker & G. Tee, *Journal of Pathology and Bacteriology*, 56, 411-415, July 1944

The authors report 6 cases of septic infection, caused by the bite of a cat or dog, from which the organism *Pasteurella* was isolated. The 3 cases of dog-bite, the first with this infection to be recorded, all occurred in the west and north-west districts of London within 3 months in the winter of 1942-43.

All the infections were characterized by severe local inflammation with pus formation and in three there was subacute osteomyelitis. The *Pasteurella* was several times found in pure culture; at other times it was accompanied by *Staphylococcus*. The three strains which were tested for animal virulence all killed when injected intraperitoneally.

Out of 4 patients' sera tested, 3 failed to agglutinate the infecting *Pasteurella* and the fourth agglutinated at a dilution of 1:80.

THE CLEANING AND STERILIZATION OF MILK BOTTLES

by B. C. Hobbs & G. S. Wilson, *Journal of Hygiene*, 43, 96-120, April 1943

G. S. Wilson, who is Professor of Bacteriology as applied to Hygiene in the University of London, and his colleague, were requested in 1937 by the British Ministry of Health to investigate the bacterial content of milk bottles after treatment in bottle-washing plants in dairies. A full report on their two years' study is available for consultation in the library of the *London School of Hygiene*; the present paper, although containing a mass of information, is only a condensed version of it.

The authors had first to devise a form of cultural test and, having tried several alternatives, decided on the addition of a measured volume of sterile 1-strength Ringer's solution to the bottle, thorough rinsing, and culturing of aliquot portions in agar. The standard of bacterial cleanliness suggested is a colony count of not more than 600 per pint bottle, i.e. about 1 colony per cm.³ of bottle capacity. Their survey embraced 105 plants of 26 different types. The lowest counts were given by bottles from large plants using detergent solutions, application of those solutions by spray being better than soaking in the solution. Steam-sterilized bottles usually gave higher counts and bottles from small hand-washing plants the highest counts of all. The authors favour the use of NaOH as a detergent, and they include data on the strengths of solution required at different temperatures. Immediately after efficient treatment with NaOH, bottles were found to be almost sterile, but subsequent rinsing with water is necessary, and this leads to re-contamination. That this explains many high bacterial counts was proved by the fact that high bottle counts were obtained from plants employing re-circulated rinse-water which itself gave such high counts that bacteria must actually have multiplied in it. If the rinse-water is kept hot enough this cannot occur, but the bottles should also be cooled before being filled. An alternative is the addition of chlorine to the rinse-water: this requires such careful control that the authors think it inadvisable.

The system proposed by the authors is new, namely: a rinse, both internal and external, in water hot enough to remain more or less bacteria-free, followed by external rinsing only with re-circulated water which cools the bottle to about 70° F. [about 21° C.]. A final spray, both external and internal, is then given with cold water direct from the main. The paper contains much valuable data and deals with many other practical points connected with the cleanliness and sterility of milk bottles.

THE SELECTIVE ACTION OF TETRATHIONATE IN BACTERIOLOGICAL MEDIA: A Report to the Medical Research Council

by R. Knox, P. G. H. Gell & M. R. Pollock, *Journal of Hygiene*, 43, 147-158, September 1943

Tetrathionate broth is commonly used as a selective enrichment-medium for the organisms of the typhoid-paratyphoid-salmonella group before plating on solid media. The method is highly successful for the isolation of *Bact. paratyphosum* B and most *Salmonellas*, but none of the suggested modifications has been so useful for the isolation of *Bact. typhosum* and the suppression of *Proteus* and Morgan's bacillus. The authors, working with the Emergency Public Health Laboratory Service, have made a careful study of the chemical changes occurring in various tetrathionate media and of the effects produced by the growth of faecal organisms in them.

The original medium of Muller (1923) contained sodium tetrathionate, which was formed by the mixture of iodine and an excess of sodium thiosulphate. The authors prepared media in which these three components were present in varying proportions and quantities. Their results are

arranged in graphic form. Any excess of iodine caused inhibition of all the organisms tested. Thiosulphate alone has a selective action, but media prepared with it inhibit the growth of the typhoid bacillus while permitting the growth of Morgan's bacillus. Good results were obtained with "balanced tetrathionate" (i.e. prepared by mixing thiosulphate and iodine in the exact quantities indicated by the chemical equation), but the medium ultimately selected for routine use was one in which thiosulphate was in slight excess, containing 25% less tetrathionate than Muller's formula. Details of the preparation of this medium are to be found in a previous paper (Knox, Gell & Pollock, 1942).

The authors made the important discovery that certain organisms, including *Bact. paratyphosum* B, most *Salmonellas*, *Bact. typhosum* (to a less marked extent) and *Proteus*, but not *Bact. coli*, *Bact. aerogenes* or the dysentery bacilli, can reduce tetrathionate to thiosulphate. This explains, in part, the selective action, as organisms able to reduce tetrathionate have a source of energy not available to the others, and their growth is therefore favoured. The increasing concentration of thiosulphate in the medium also explains why subculture of tetrathionate broth cultures at different intervals of time produces varying results. The reaction involves the production of high acidity which must be controlled by the use of chalk or phosphate as a buffer. Both these substances favour the growth of *Proteus* and Morgan's bacillus, so that the ideal tetrathionate medium has clearly not yet been devised.

The study of solid tetrathionate media gave interesting results. Where thiosulphate is present in excess, the medium becomes opaque. Colonies of *Bact. paratyphosum* B are surrounded by a clear and striking zone of "lysis" caused by bacterial reduction of the tetrathionate. Practical use of these media could not be made, however, as they are too inhibitory to *Bact. typhosum*. The authors recommend a solid medium containing balanced tetrathionate in a concentration of 0.03 molar. This medium has given excellent results in the isolation of typhoid and paratyphoid bacilli and several strains of *Salmonella*. It is highly selective, but recognition of colonies requires some experience.

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THE LABORATORY DIAGNOSIS OF DIPHTHERIA: A Note on some Present-day Methods

by H. A. Wright, *Edinburgh Medical Journal*, 50, 737-745, December 1943

The author, who is a member of the bacteriological staff of the University of Edinburgh, discusses some of the difficulties in the laboratory diagnosis of diphtheria, and describes the modifications of technique which have now become current practice in Britain. Modern knowledge demands the use of selective culture-media containing tellurite, and the recognition of the different types of diphtheria bacillus.

It is still customary to inoculate swabs on Loeffler's serum slopes, for this medium promotes the rapid growth of *C. diphtheriae* and good development of metachromatic granules, and will give a positive result with most clinical cases. Swabs from contacts, carriers, and convalescents, however, frequently give negative results on this medium, and this may also happen in mild clinical cases or in severe cases in which other organisms are abundant. Further, the *gravis* type may be difficult to recognize on Loeffler's medium. Petri-dish culture on one of the media containing tellurite, such as that of Anderson, Happold, McLeod & Thomson (1931) or Hoyle (1941), is therefore essential.

Tellurite media inhibit the growth of many organisms common in the throat and nose, and permit the identification of the three types of diphtheria bacilli, *gravis*, *mitis* and *intermedius*, a differentiation which is of considerable epidemiological and clinical interest. The plates are inspected after 18 hours' incubation, but a negative report should be given only after 48 hours, as some strains may be slow to develop. With a low magnification, the dull slate-grey radially striated *gravis* colonies, the smooth round low-domed *mitis* colonies, and the much smaller dark regular colonies of the *intermedius* type can be recognized. Microscopic morphology of

* [see also BMB 572 & 573].

diphtheria bacilli from tellurite media can be learned by experience, and the barred forms of the *intermedius* strains are typical. Further biochemical reactions, such as the fermentation of starch by *gravis* strains, complete the typing of diphtheria bacilli.

The bacteriologist appreciates the desire of the clinician for an early and unequivocal report, and this is usually possible in clinical cases, but it must be understood, by the medical officer of health and the hospital administrator particularly, that an accurate final report may be available only after investigations which inevitably take two days, or even longer, to perform.

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600

THE FILTRATION OF *MYCOBACTERIUM TUBERCULOSIS* AND *MYCOBACTERIUM STERCUSIS* THROUGH GRADOCOL MEMBRANES

by M. A. Soltys & A. W. Taylor, *Journal of Pathology and Bacteriology*, **56**, 173-180, April 1944

A number of workers have maintained that the life cycle of *Myco. tuberculosis* might include a stage at which viable organisms could pass through filters which would hold back ordinary tubercle bacilli. They claimed that such filtrates, though free of tubercle bacilli of the usual form, would produce a modified tuberculous infection in experimental animals. As the technical difficulties of this kind of work are very great, considerable scepticism has been expressed as to the validity of their results. The evidence is discussed by Topley & Wilson (1936). Various types of filter have been used, but in only one previous paper was work with a filter of known pore size—0.4 μ —described. There was no evidence that a viable form of the tubercle bacillus could pass through this filter (Lewis, Ruckman & James, 1934-35). In the present paper the problem is re-examined by two workers at the *Moredun* Institute, Gilmerton, Midlothian.

Technical methods. Three types of material containing tubercle bacilli were used: (i) cultures of human and bovine *Myco. tuberculosis* from 1 to 35 days old; (ii) lungs and spleens from rabbits dying of experimental bovine tuberculosis, and lymph nodes and lungs from naturally infected cattle; (iii) sputum rich in tubercle bacilli from patients with pulmonary tuberculosis. Cultures of *Myco. stercusis* were also used. The material was ground or shaken with Tyrode's solution [a physiological solution of salts and glucose] to give an appropriate suspension. Preliminary filtrations were made, first through paper pulp and then through Kieselguhr [a preparation of diatomaceous earth].

A culture of louping-ill virus, centrifuged and filtered through Kieselguhr, was mixed with the suspension of tuberculous material as a control for the patency of the filter; 0.1 cm.³ of the filtrates was injected intracranially into mice and in every experiment produced typical louping-ill.

The filters were gradocol membranes supplied by St. Mary's Hospital, London, and were of 4 sizes, having a pore-diameter of 2.02 (or 1.95), 1.5 (or 1.43), 1.00 and 0.7 (or 0.69) μ respectively.

Filtration was performed by applying a negative pressure of about 30 cm. Hg for $\frac{1}{2}$ to 1 minute. Each suspension was passed successively through filters of the 4 sizes, samples of each filtrate being taken for testing.

The filtrates were examined for tubercle bacilli by the injection of 3.5 cm.³ intraperitoneally and subcutaneously respectively into two guinea-pigs. *Myco. stercusis* was demonstrated by culture.

The results can be summarized as follows:

- i. The bovine type of *Myco. tuberculosis* did not pass through pores of 0.7 (or 0.69) μ diameter in 5 experiments or pores of 1.00 μ in 3 experiments.
 - ii. The human type of *Myco. tuberculosis* did not pass through pores of 1.00 μ in any one of the 4 experiments performed.
 - iii. Suspensions of *Myco. stercusis* at 4 dilutions from 1:50 to 1:10,000 did not pass through pores of 1.03 μ diameter.
- In the words of the authors—"No evidence was obtained which might have suggested the existence of a form of these organisms in any way analogous to an ultraviable virus."

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601

AN APPARATUS FOR THE SAFE INOCULATION OF ANIMALS WITH DANGEROUS PATHOGENS

by M. van den Ende, *Journal of Hygiene*, **43**, 189-195, September 1943

Work in the laboratory with certain bacteria, as for example the *Brucella* group, and certain viruses such as psittacosis, has long been recognized as involving undue risk of infection for the bacteriologist. This danger is liable to be particularly great when experimental infection of animals by the intranasal route is practised; recent experience has shown that the hazard is a very real one when nasal instillation of typhus rickettsiae is made into anaesthetized mice. The apparatus described by Dr. M. van den Ende from the National Institute of Medical Research at Hampstead, London, is designed to overcome this risk. It consists essentially of a steel-and-glass box, inside which the inoculation of the mice is carried out. The anaesthetized mice are passed into the box through an opening in the left side which can be closed by a sliding door. After inoculation they are placed into labelled glass jars held in the right half of the box. The operator wears a surgical gown and rubber gloves and his hands are introduced into the box through rubber sleeves fitted into the front of the box. An essential feature of the apparatus is that draught ventilation through the box is provided by a gas burner in the chimney attached to the box. This prevents the escape of infected droplets from the box during the manipulation of the mice. Above the burner the chimney is so constructed that all air drawn up the chimney is effectively heated. After the mice have been inoculated, they are left in the box for 45-90 minutes, during which period quartz-jacketed ultra-violet lamps inside the box are turned on. The mice are then transferred to cages and the glass jars are immediately sterilized. The construction of the box is described in detail, with the aid of diagrams, in an appendix by A. J. G. Hubbard.

Experiments were made, using *Chr. prodigiosum* as an indicator organism, to determine the degree of aerial infection during intranasal inoculation of mice, and the effect of the chimney furnace and ultra-violet rays on the numbers of infective droplets distributed into the air of the apparatus by inoculated mice. When inoculated mice were kept in the box while the chimney furnace and ultra-violet lamps were not in operation, infected particles were recovered from the air up to 40-45 minutes after inoculation. Ultra-violet rays reduced the number of particles significantly, but the chimney was more effective. The chimney alone was capable of clearing the air in the box almost completely within 7 minutes after the introduction of a heavy spray of bacteria-laden particles. That the draught through the box was effective in preventing infected particles from passing outside the box was shown by sampling the air outside the open door in the end of the box when numerous infected droplets were present inside.

Since the introduction of the apparatus for typhus work in the author's laboratory, only one case of typhus has occurred in 4 months among 8 individuals working on this disease; before the box was introduced several workers contracted typhus within a month of commencing work involving the intranasal inoculation of rickettsiae into mice.

Various Bacteriological Studies

602

THE NATURE AND MODE OF ACTION OF STAPHYLOCOCCUS COAGULASE

by W. Smith & J. H. Hale, *British Journal of Experimental Pathology*, **25**, 101-110, June 1944

It has been known for many years that some strains of *Staphylococcus* produce a substance which will cause the

clotting of plasma. Recently this property has been utilized by the bacteriologist in assessing the pathogenicity of strains of *Staphylococcus*, as the substance, coagulase, is seldom produced by non-pathogenic strains (Chapman, Berens, Peters & Curcio, 1934; Christie & Keogh, 1940; Cadness-Graves, Williams, Harper & Miles, 1943).

In routine bacteriological testing, citrated human plasma diluted 1/10 is usually used, but occasional human plasmas are encountered in which no clot, or an incomplete clot, is formed. Rabbit or horse plasma may replace human plasma, but guinea-pig, mouse and fowl plasmas do not clot under the conditions of the test. These individual and species differences, as well as the fact that human fibrinogen after it has been purified by repeated precipitation is not clotted by coagulase, were anomalies which the present work explains. It was carried out in the Department of Bacteriology of Sheffield University.

In preliminary experiments the authors showed that coagulase would pass without loss through a "gradocol" membrane with a pore diameter of 0.50 μ , though retained completely by one with a pore diameter of 0.11 μ . It was relatively heat-stable, as only partial loss occurred in 30 minutes at 80° C. Having established these data, they were able to make sterile concentrated preparations of coagulase by filtration and distillation at 60–70° C. under reduced pressure; with these preparations the remaining work was carried out.

They first ascertained that in the clotting of normal blood all the factors concerned were interchangeable between different species, thus showing it to be highly improbable that differences in the structure of the fibrinogen accounted for the differences in coagulase action in the various species. In the course of this work they discovered that the addition of a testis extract containing thrombokinase (prepared by grinding with distilled water, centrifuging and filtering) to the coagulase-plasma mixture produced clotting in otherwise incoagulable plasmas. Hence it was clear that a second substance, lacking in these plasmas and necessary for the action of coagulase, was provided by the testis extract. Guinea-pig testis was much less effective in activating coagulase than human or rabbit testis, though it was equally rich in thrombokinase. This strongly suggested that the substance which activated prothrombin was different from that which activated coagulase.

A sample of "incoagulable" human plasma was shown to contain small amounts of activator, being clotted by a dilution of coagulase of 1/40, instead of 1/640 which was effective for typical plasma. With both typical and atypical plasmas, the time required for clotting increased with increasing dilution of the coagulase. At the higher dilutions (e.g. 1/50 and over), even the typical plasma clotted with increasing speed if increasing amounts of testis extract were added, while with both plasmas a really large amount of coagulase (1/10 dilution) caused rapid clotting without regard to added activator. The clotting time of highly diluted typical plasma (e.g. 1/50) was greatly reduced by adding testis extract. Thus it appeared that even typical plasmas do not contain activator substance in optimal amount for all doses of coagulase, that a sufficiently large dose of coagulase will compensate for deficiency of activator, and that the prolonged clotting time of highly diluted plasma is due at least in part to the dilution of activator.

The fibrinogen-prothrombin complex of blood can be extracted free of kinase by dilution and acidification of plasma or by repeated precipitation with ammonium sulphate. Such preparations are clotted by coagulase only if activator, e.g. in testis extract, is added.

The combination of coagulase with activator, which may be considered analogous to the combination of prothrombin with kinase, was shown by serial sampling of a mixture of coagulase and testis-extract to be a slow process compared to the rapid activation of prothrombin. Both activator and the activator-coagulase complex were shown to be heat-labile, in contrast with coagulase, which is heat-stable. These facts taken together explain the apparent anomaly that guinea-pig plasma is slowly clotted by coagulase at 20° C., though not at all at 37° C. The small amounts of activator in the plasma react slowly with the coagulase and eventually produce clotting, but only if destruction of the complex is reduced by keeping the mixture cool. Many experiments designed to elucidate the anomaly all supported this explanation.

Thrombokinase and the coagulase activator, both present in testis extracts, can be separated by dialysis, which removes the kinase, or by heat in the absence of electrolytes, which destroys the activator.

From this careful and complete work the authors conclude that coagulase cannot itself convert fibrinogen to fibrin, but that it requires the participation of an activator which is present in adequate amounts in some plasmas but deficient or lacking in others. Further work in progress is being directed towards concentrating the activator and investigating its nature.

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- ² [see *BMB* 148]

603

RELATIVE STERILITY OF THE HANDS OF CERTAIN METAL WORKERS

by I. Lominski & G. R. Thomson, *British Journal of Industrial Medicine*, **1**, 165–167, July 1944

In this short paper from the Departments of Bacteriology and Surgery, Glasgow University, and the Western Infirmary, Glasgow, the authors demonstrate that certain types of work with metals lead to a great reduction in the number of micro-organisms on the skin of the exposed parts of the hands and arms. The workers concerned were handling metal filings mixed with oil, the filings comprising copper, manganese, iron and other elements. Contact with filings alone or with oil alone did not have any sterilizing effect.

Methods: The hygienic conditions and exact occupation of each worker were investigated with great care; those in contact with such substances as bleaching agents, paints and antiseptic soaps were excluded. Forty workers handling metal filings with oil, in whom full and satisfactory investigations were made, were compared with a control group of 86 from various other occupations, including 12 metal workers not in contact with both filings and oil, 22 carpenters and 17 doctors and nurses. With few exceptions the 40 workers in metal filings with oil had only one bath a week and only one hand-wash a day.

At least 2 hours was allowed to elapse between hand-washing and taking the bacteriological samples. Six swabs which had been soaked in sterile saline were used for each individual; areas about an inch square on the right palm, back of hand and outer side of forearm were each rubbed successively with two swabs, and each swab was inoculated on to two blood-agar plates. Colony counts were made and averaged for the 4 plates inoculated from each area. In about 50% of individuals, sampling was repeated after 2 weeks; these results were closely similar and were averaged with the first counts.

Results: The statistical analysis was made on the swabs from the palm, since these were less often sterile and showed less variation in one individual than those from other sites. The counts were classified into 11 groups according to the number of colonies; groups 0–2 contained 0–25 colonies; 3–5, 26–250 colonies; and 6–10, 251 colonies to 5,000 or more. Of the 40 workers in metal filings with oil, 87.5% fell into groups 0–2, and all were in groups 0–5; 12 (30%) gave sterile swabs. Among the controls there were no sterile swabs and 59.2% fell into groups 4–6 (51–500 colonies). Taking group 2 as the limit of "cleanness" it is shown that:

- i. the proportion of "clean" individuals among workers in metal filings with oil = 87.5%; among control population = 13.9%;
- ii. the percentage difference between the two populations = 73.6%;
- iii. this difference is 11.46 times the standard error, which = 6.42%.

In discussion, the authors suggest that this relative sterility arises from the accumulation of fine metal particles in sensitive organisms. They point out also that carpenters showed a slight relative sterility compared with other control groups, and attribute this to antibacterial action by the moulds and related organisms present in wood.

THE BACTERIOLOGY OF BRAIN ABSCESS

by A. M. McFarlan, *British Medical Journal*, 2, 643-644, 20/11/43

Dr. A. M. McFarlan, a member of the Emergency Public Health Laboratory Service, reports here a study of the bacteriology of brain abscess, made on behalf of the *Medical Research Council*. He points out that, as the patients had all been referred to neurosurgical clinics, the study does not include fulminating cases, which might present a different bacteriological picture.

Of the 48 patients studied, 36 were male and 12 female; their ages were distributed between 5 and 53 years, with 24 cases between 20 and 40 years of age. Among probable sources of infection ear-disease predominated, accounting for 18 cases.

Films of the pus were stained by Gram and Ziehl-Neelsen methods. In all cases aerobic and anaerobic cultures were made on horse-blood agar plates and in ox-serum broth. When examination suggested the need for enriched or selective media Fildes's agar, 20% ox-serum agar, or horse-blood agar with crystal violet (1 in 500,000) or sodium azide (1 in 1,000) were used.

One abscess showed no organisms in films and was sterile on culture. Of the remaining 47, 33 showed a single organism and 14 more than one. The commonest organism was *Staph. aureus*, found in 15 abscesses (in pure culture in 13) distributed evenly through the various age-groups. All strains were coagulase-positive. Anaerobic streptococci were found in 10 abscesses (in pure culture in 1) and fusiform bacilli with varying biochemical and cultural characters in 10 (in pure culture in 2). The other organisms found (the number of times in pure culture is given in parentheses) were—*Strept. pneumoniae* 6 (6) of which 4 grew only anaerobically in the primary cultures; *Strept. pyogenes* 4 (4), all of group A (Lancefield); *Strept. viridans* 2 (1); non-haemolytic and unclassified streptococci 5 (2); *Proteus vulgaris* 6 (2); anaerobic diphtheroids 2 (0); *Micrococcus tetragenus* 1 (1); and *H. influenzae*, seen alone in films once, but not grown in culture.

The author notes that though streptococci were common they were of several different types which could not justifiably be classed together; the staphylococcus therefore was the commonest single organism. The finding of anaerobic streptococci and pneumococci as well as of anaerobic fusiform bacilli and diphtheroids indicates the importance of making anaerobic cultures when investigating brain abscesses. The author points out that it is consonant with experimental work (Wámoscher & Vásárhelyi, 1933; Falconer, McFarlan & Russell, 1943) to suggest that brain abscesses due to anaerobic organisms originate in foci of lowered oxidation-reduction potential (Fildes, 1927) produced by a vascular accident or by aerobic organisms which later die out.

A careful study was made of the degree of encapsulation of the abscesses, but as this was found to vary greatly between the superficial and deep parts even of the same abscess no conclusions could be drawn as to whether encapsulation and bacterial flora were correlated. Anaerobic and Gram-negative bacilli were several times found in abscesses with a well-developed capsule.

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BIOCHEMICAL CLASSIFICATION OF COLIFORM BACILLI IN SPUTUM

by R. Salm, *Edinburgh Medical Journal*, 51, 247-251, May 1944

The author, working in the Bacteriological Department of the Royal Infirmary, Edinburgh, made a systematic classification of the coliform bacilli found in sputum. About 1 sputum in 5 yielded coliform organisms, and 100 coliform strains were isolated from 80 sputa. The primary isolation was made from blood-agar and McConkey plates, after incubation for 48 hours.

Coliform bacilli cannot be grouped serologically, as an antiserum seldom agglutinates any strain except that used to prepare it. Pathogenicity to animals is variable. Classification must therefore depend on *in vitro* biochemical reactions, and in this work the following were used: fermentation of glucose, lactose, dulcitol, saccharose, mannite, maltose, adonite and inositol; changes in litmus-milk and gelatine; and the "Imvic" reactions, that is (i) indol test, (ii) methyl-red test, (iii) Voges-Proskauer reaction (O'Meara's modification) and (iv) Koser's citrate-utilization test. All the media were incubated at 37° C. for 48 hours, except gelatine which was kept at room-temperature for 2 months.

The strains were classified into 7 groups:

1. *B. coli*. Thirteen strains fell into this group, which consisted of those which gave the 4 "Imvic" reactions (in the above order) as ++--. All fermented glucose, lactose, mannite and maltose with production of acid and gas, and 9 were motile.

2. *B. anaerogenes*. Distinguished by the fermentation of two or more sugars with production of acid only. Seven strains fell into this group. Five were motile, and 3 liquefied gelatine.

3. *B. proteus-morgani*. Distinguished by fermenting only glucose. Eleven strains, of which 3 produced acid and gas, and the rest gas only. Six liquefied gelatine. Voges-Proskauer negative in all.

4. *B. pyocyaneus*. Distinguished by production of blue-green pigment. Five strains, all motile, fermented glucose with production of acid only, and liquefied gelatine. "Imvic" reactions ---+ were the same for all.

5. *B. faecalis alkaligenes*. Distinguished by not fermenting any sugar. Eight strains, only two of which were motile.

6. *B. friedländer-aerogenes*. This group consisted either of strains which fermented adonite and/or inositol with production of acid or acid and gas, or of those which gave "Imvic" reactions --+++. Thirty strains fell into the group, of which 17 were mucoid and 7 were motile. Maltose was fermented by all and mannite by all but one; 11 fermented litmus-milk with acid, and 2 with acid and clot; 7 liquefied gelatine. Two of the motile strains gave the above "Imvic" reactions, which are characteristic of true *B. aerogenes*.

7. *B. coli intermedius*. In this group were placed all strains which could not be classified in 1-6. Twenty-five strains; 14 showed motility, 10 liquefied gelatine, 12 fermented milk with acid and 5 with acid and clot. 5 did not ferment lactose. The "Imvic" reactions varied, though all strains gave methyl-red +. They resembled the *B. coli* group in all respects except that the "Imvic" reaction ++-- was by definition excluded.

In addition, one strain which was indistinguishable from a coliform bacillus on primary culture became partially Gram-positive in subculture and proved to be a leptothrix.

In discussion, the author points out that, although the classification was in some respects arbitrary, the great majority of strains fell definitely into one group or another.

BOOKS, MEMORANDA, REPORTS

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606/89

A HISTORY OF COMPARATIVE ANATOMY

From Aristotle to the Eighteenth Century

by F. J. Cole. London, Macmillan & Co. Ltd., 1944. 524 pages ; 200 illustrations. £1 10s. [£1.5]

History books too often prove to be compilations of what is already known, with, perhaps, a little additional matter to bring the work up to date. It is, therefore, especially pleasing to record the appearance of this book, which shows evidence of much original research on the part of the writer. Professor Cole is a former holder of the chair of zoology in the University of Reading and enjoys a world-wide reputation as an authority on the history of zoology. Comparative anatomists, zoologists, and in fact all who are interested in the history of the biological sciences, will welcome this critical review, which traces the development of comparative anatomy from the time of Aristotle to the beginning of the eighteenth century. Although the material is arranged chiefly under the various comparative anatomists, biographical detail is reduced to a minimum and relegated to an appendix, for, as the author himself reminds us, this aspect is one which has been traversed so often before that it is more profitable to confine the text of such a book as this to material which has hitherto partly or wholly escaped attention. This does not mean that the biographical material is inadequate or that the work of the more eminent comparative anatomists receives insufficient attention. The whole story is told and the records of fundamental achievements are linked together with less well-known but nevertheless important developments. The writer has obviously sought widely for his material and has succeeded both in bringing to light some new facts and in correcting some errors. The book is extremely well written and includes some excellent illustrations, a number of which are not easily available elsewhere. There is a useful appendix of biographical notes on all important comparative anatomists, a well-selected bibliography and a full index.

After an introductory chapter on first statements of the comparative method, the remaining 34 chapters are arranged in the following groups: (i) the contribution of Greece; (ii) zootomy down to the sixteenth century; (iii) the development of craftsmanship; (iv) Harvey; the encyclopaedists; (v) the new comparative anatomy; (vi) the Dutch school; (vii) academies and societies; the anatomy lesson; (viii) the anatomical museum.

Professor Cole is to be congratulated on the completion of this scholarly work, which will take a permanent place in the literature on the history of science. We can but hope that he will one day provide us with a second volume, bringing the story up to the present day.

606/90

A GUIDE FOR THE TUBERCULOUS PATIENT

by G. S. Erwin. London, William Heinemann (Medical Books) Ltd., 1944. 115 pages. 3s. 6d. [£0.175]

Tuberculosis is one of those diseases in which the intelligent co-operation of the patient is essential, both during and after treatment. For this reason it is necessary to explain to him the cause, methods of diagnosis and treatment, and how he can live safely after the period of his treatment has been completed. Just such an explanation is provided by this book, written by the medical superintendent of Liverpool Sanatorium. As the author points out, the tuberculous patient undergoing treatment hears and comes to use many of the technical terms in daily use around him; such knowledge makes further reading less difficult. The patient who is anxious to learn more about his disease and to co-operate to the full in his treatment will find this book a most useful guide. The writer is careful to explain the meaning of all technical terms employed in the book, and in ten short chapters he discusses (i) the causes of tuberculosis; (ii) how the disease is discovered; (iii) complications; (iv) treatment, general; (v) treatment, special; (vi) home and institutional treatment; (vii) the post-sanatorium régime; (viii) miscellaneous information; (ix) legal and other aspects; (x) non-pulmonary tuberculosis. Particular care has been taken in explaining the post-sanatorium régime, and the physician can safely prescribe this book for his tuberculous patients.

606/91

MINOR SURGERY

by R. J. McNeill Love. 2nd edition. London, H. K. Lewis & Co., Ltd., 1944. 392 pages; 201 illustrations. 15s. [£0.75]

All those practical procedures which can be regarded as "minor" surgical operations are described by Mr. Love and his collaborators. Attention is first of all given to the examination of the patient, and diagnostic procedures capable of being carried out in the consulting-room are described. Sections on antisepsis and asepsis are followed by a description of wound toilet. The principal bandages are described; there is a section on the treatment of

hernia. The chapter on minor surgical operations includes descriptions of blood transfusion, shock and resuscitation, cysts, bursae, tumours, dental extractions, tonsillectomy, removal of adenoids, abdominal paracentesis, the treatment of hæmorrhoids, infections of the hand and foot, amputations. A quarter of the book is devoted to fractures and dislocations, and this contains some excellent illustrations. The book, which is intended as a guide to hospital residents and general practitioners called upon to deal with minor surgical problems and common surgical emergencies, is well produced and profusely illustrated.

Chapter headings: (i) examination of the patient; (ii) antisepsis and asepsis; (iii) preparation of a patient for operation; the operation, after-treatment; (iv) wounds; (v) the vascular system; (vi) cellulitis and abscess; (vii) bandaging, slings, knots, strapping; (viii) hernia; (ix) minor surgical operations (by R. E. Norrish and A. W. Bone); (x) genito-urinary surgery (by A. W. Badenoch); (xi) the eye and ear; (xii) anaesthetics (by D. Blatchley); (xiii) fractures and dislocations (by F. P. Fitzgerald).

606/92

A MANUAL OF DISEASES OF THE EYE

by C. H. May & the late C. Worth. 9th edition, revised by M. L. Hine. London, Baillière, Tindall & Cox, 1944. 538 pages; 371 illustrations. 16s. [£0.8]

This is a concise, practical manual of the diseases of the eye, arranged on systematic lines and intended for the student and the general practitioner rather than the specialist. Whilst it gives all the essential facts on ophthalmology and describes fully the common diseases of the eye, rare conditions and uncommon affections are dealt with as briefly as possible. Notable in the sections on treatment are the incorporation of work on sulphonamide and penicillin therapy, which are becoming increasingly important in ophthalmic practice. Careful consideration is given to vitamin therapy, and attention is called to some tests for dark adaptation, which have come into greater prominence under wartime conditions. Many other changes have been made in this edition, bringing it up to date and in full accord with modern teaching. A number of the illustrations are in colour.

Chapter headings: (i) examination of the eye; (ii) subjective or functional examination of the eye; (iii) objective examination of the eye conducted in the dark-room; (iv) the slit-lamp and corneal microscope; (v) affections of the eyelids; (vi) diseases of the lacrimal apparatus; (vii) diseases of the orbit; (viii) diseases of the conjunctiva; (ix) diseases of the cornea; (x) diseases of the sclera; (xi) diseases of the iris; (xii) diseases of the ciliary body; (xiii) diseases of the choroid; (xiv) intra-ocular tumours; (xv) glaucoma; (xvi) diseases of the vitreous; (xvii) affections of the lens; (xviii) diseases of the retina; (xix) diseases of the optic nerve; (xx) amblyopia and functional affections of the retina; (xxi) general optical principles; (xxii) optical consideration of the eye; (xxiii) errors of refraction; (xxiv) paralyses of external ocular muscles; (xxv) comitant squint; (xxvi) heterophoria; (xxvii) operations on the external ocular muscles; (xxviii) the ocular manifestations of general diseases; (xxix) ophthalmology in the tropics; (xxx) ocular therapeutics; general rules for operations upon the eye; (xxxi) eye injuries in war time; (xxxii) visual requirements for British and Indian public services.

606/93

AIDS TO CLINICAL PATHOLOGY

Including Post-Mortem Technique

by D. Haler. London, Baillière, Tindall & Cox, 1944. 358 pages. 6s. [£0.3]

This small book is an up-to-date combination of two earlier volumes in this series, *Aids to pathological technique* and *Aids to practical pathology*. It has been compiled by the honorary pathologist to All Saints' Hospital, London, and is intended for students and others interested in laboratory work. It describes in detail the more common laboratory diagnostic procedures; space does not permit the inclusion of details of the more refined haematological procedures or of the grouping of streptococci. Students embarking on the study of clinical pathology will find this useful as an introduction to the subject and for revision purposes. It is particularly important that medical terms in books used by students should be accurate. Unfortunately a number of minor errors have crept into this book; a cursory glance reveals sulphoni/amides, Charcot-Leydin, Fildes, Kleb, Schultze-Charlton, *H. pertussis*, Volhardt, Pettenköpfer, Krunkenberg and Krunkenberg, Lancefeld, *F. bancroftii*, Kerne-ikterus. However, the book fills a need and such errors will no doubt be corrected in future editions. It is divided into 54 short chapters, grouped into the following sections: (i) post-mortem technique; (ii) haematology; (iii) cytology; (iv) histology; (v) bacteriology; (vi) serology; (vii) parasitology; (viii) biochemistry.

THE RECORDING OF SICKNESS ABSENCE IN INDUSTRY

(A Preliminary Report)

by A Sub-Committee of the Industrial Health Research Board.
Medical Research Council, Industrial Research Board Report No. 85.
London, H.M. Stationery Office, 1944. 17 pages. 4d. [£0.016]

The recording of sickness absence in industry makes it possible for industrial organizations to determine the effective labour strength (as opposed to book strength) of their staffs, and enables a check to be kept on the effects of conditions of work on the health of those employed in the various departments of the factory, shop or office.

The *Industrial Health Research Board* has considered various methods of recording absence due to sickness and has suggested a uniform method of recording sickness rates in order to enable valid statistical comparison to be made. After discussing the value of health and sickness records, the report outlines methods of obtaining information and of recording sickness absence. The compilation of a sickness absence record is suggested, to give a monthly, quarterly or annual summary. Sickness absence should be grouped as far as possible into those classes of disease which may have some relation to the working environment, and a nomenclature of diseases for the classification of certified sickness and accidents is provided in the report.

606/95

THE VENEREAL DISEASES

A Manual for Practitioners and Students

by James Marshall. London. Macmillan & Co. Ltd., 1944. 348 pages ; 8 coloured plates and 105 illustrations. £1 1s. [£1.05]

The author of this work, who is venereologist to the Eastern Command and a former medical officer of the London Lock Hospital, considers that the time is ripe for a general review of the methods of diagnosis and treatment of the venereal diseases. He believes that the average case of venereal disease may well be treated in private practice, and he has, therefore, prepared this full account of methods most suitable for such a purpose.

The various manifestations of venereal and allied diseases are described. Recent advances in the chemotherapy of venereal disease promise more rapid methods of treatment, and the author includes an outline of the experimental work on massive arsenotherapy for syphilis. It is unfortunate that this book was printed before full details of the results of clinical trials with penicillin had become available. It is possible that penicillin, or a similar antibiotic, will prove to be the chemotherapeutic agent *par excellence* for both gonorrhoea and syphilis. Although in syphilis penicillin may supersede massive arsenotherapy, this latter form of treatment has proved very successful, but requires hospitalization of the patient. Modern methods of fever therapy are also described. The sulphonamides, which have become important in the treatment of gonorrhoea, are fully discussed ; owing to present difficulties of supply, the author has devoted more space to sulphapyridine than to sulphathiazole and sulphadiazine, although the last two are to be preferred. In the descriptions of routine treatment alternative schemes are avoided as far as possible.

Chapter headings : Part I, gonorrhoea : (i) introduction, (ii-iii) gonorrhoea in the male, (iv) gonorrhoea in the female, (v) aspects of gonorrhoea common to both sexes, (vi) vulvovaginitis in children, (vii) urethral stricture, (viii) the sulphonamides ; Part II, syphilis : (ix) introduction, (x) diagnosis, (xi-xii) early syphilis, (xiii-xv) late syphilis, (xvi) congenital syphilis, (xvii-xviii) treatment, (xix) prognosis ; Part III, other venereal and allied diseases : (xx) rarer venereal diseases, (xxi) other diseases encountered in venereology ; Part IV, technique : (xxii) practical instructions. There are, in addition, appendices on (i) sociology of venereal diseases, and (ii) list of special equipment ; and a short bibliography. The book is well illustrated and includes 8 coloured plates.

606/96

LOCAL ANÆSTHESIA : BRACHIAL PLEXUS

by R. R. Macintosh & W. W. Mushin. Oxford, Blackwell Scientific Publications Ltd., 1944. 56 pages ; 33 illustrations. 10s. 6d. [£0.525]

Until 1940 the main disadvantage of brachial plexus block was the uncertainty of success. In that year Patrick described a technique which for the first time enabled the procedure to be undertaken with the assurance that anaesthesia would result. The monograph now under review is written by two members of the Nuffield Department of Anaesthetics in the University of Oxford, and they have based their work on Patrick's method. All the deep structures of the upper extremity, and the skin distal to the middle of the upper arm, are rendered insensitive by brachial plexus block.

After a brief description of the pioneer work of Halsted, Crile, Hirschel and Kulenkampff in the anaesthetization of this region, the authors discuss its indications and advantages, and describe in detail the anatomy of the supraclavicular area and their own technique for the supraclavicular injection of the brachial plexus. The technique is one in which, as the authors themselves point out, the main instruction is better conveyed by pictures than by the printed word and, while the text lacks nothing in detail, the illustrations, beautifully drawn by Miss M. McLarty, are an outstanding feature of this little book. Many are in colour and all,

like the text, are well produced on excellent paper. The book is fortified by a few important references to the literature. Its brevity and lucidity make it an excellent example of the short medical monograph ; it is an important contribution to the literature on anaesthesia.

606/97

AIDS TO THEATRE TECHNIQUE

by M. Houghton & M. Harding. London, Baillière, Tindall & Cox, 1944. 262 pages ; illustrated. 4s. [£0.2]

This latest addition to the *Nurses' Aids* series of small textbooks has been compiled by the sister tutor and the senior theatre sister of *University College Hospital*, London. A good memory and an extensive experience of theatre technique are essential in the theatre nurse, and this little book provides a satisfactory basis on which the student nurse can build her knowledge of theatre instruments and appliances ; it will also serve as an aid to memory for the qualified nurse who, without previous theatre experience, may find herself confronted with the task of preparing for an emergency operation. The illustrations are a notable feature of the book ; in the chapters on surgical operations are depicted trolleys completely equipped for various operative procedures. The more common positions of the patient on the operating table are also well illustrated. The book is well printed in small but clear type, on good paper. A great deal of useful information is incorporated in its 21 chapters ; a glossary of instruments and a full index are provided.

606/98

THE MEDICAL ANNUAL, 1944

edited by Sir Henry Tidy & A. Rendle Short. Bristol, John Wright & Sons Ltd., 1944. 404 pages ; 40 plates. £1 5s. [£1.25]

This publication, now in its 62nd year, is an annual review of medical and surgical progress, a digest of the important literature of the world during the previous year. It appeals particularly to general practitioners and others as a means of keeping abreast of recent progress. The very comprehensive series of articles on many subjects is compiled by 41 eminent medical and surgical authorities in Britain. In their introduction, the editors record a number of topics which have aroused more than usual interest during the year under review. We may mention the particular attention paid to infective hepatitis, epidemic nausea and vomiting, mass miniature radiography, rehabilitation. As is to be expected, a great deal has been written during the year on war surgery. An article on ageing (geriatrics) is of interest as indicating the increasing attention which must be given to the problems of old age. Although much had been written on penicillin therapy before this book was prepared, no separate article is devoted to the drug.

606/99

PYE'S SURGICAL HANDICRAFT

A Manual of Surgical Manipulations, Minor Surgery, and Other Matters Connected with the Work of Surgical Dressers, House Surgeons, and Practitioners

edited by Hamilton Bailey. 14th edition. Bristol, John Wright & Sons Ltd., 1944. 628 pages ; 724 illustrations. £1 5s. [£1.25]

Pye has been in existence since Lister's day and with the appearance of this fourteenth edition, celebrates its sixtieth birthday. We can recall only one other British medical book (*Gray's Anatomy*) which has survived as long. This edition is a collective work of 80 chapters, contributed by 46 authorities under the editorship of Hamilton Bailey. The editor himself is responsible for numerous chapters, but his most notable contribution is perhaps the profusion of excellent illustrations, an important feature in other works from his pen. A number of these illustrations are in colour ; all have been carefully selected with a view to illustrating the technical procedures involved in minor surgery.

Each subject has been carefully revised by its contributor. The advantage of individual contributors for special subjects is obvious, and nowhere better illustrated than in this book, which has the added advantage of expert editorship. Production is of the highest standard, and the index is, as usual, excellent.

This book is an essential tool for the house surgeon and a valuable post-graduate education for the general practitioner.

606/100

A TEXT-BOOK OF GYNÆCOLOGY for Students and Practitioners

by James Young. Sixth edition. London, A. & C. Black. 1944. 443 pages ; 255 illustrations. £1 5s. [£1.25]

This text-book is by the director of the obstetrical and gynaecological unit at the *British Postgraduate Medical School*, who is also professor of obstetrics and gynaecology in the University of London. Besides giving a comprehensive orthodox account of the subject, the book has in the past been noted for its good description of the physiology of menstruation and the sex hormones. A complete revision, both of text and illustrations, has brought this new edition completely up to date and in line with modern teaching. Fifty-seven excellent new illustrations have been added, and some old ones discarded. This is an excellent short text-book of the subject.

Chapter headings: (i) external genital organs, vagina; (ii) uterus, uterine ligaments, pelvic floor; (iii) fallopian tubes, ovaries, parovarium; (iv-vi) menstruation; (vii-viii) history, physical examination; (ix-xi) disorders of menstruation; (xii) the menopause and its disorders; (xiii) disorders of function of procreation, dyspareunia, sterility; (xiv) leucorrhœa; (xv) pain in gynaecology; (xvi) symptoms relating to the urinary system in gynaecology; (xvii) symptoms relating to the gastro-intestinal tract in gynaecology; (xviii) anterior displacements of the uterus, acute ante-flexion; (xix) backward displacements of uterus; (xx) genital prolapse, prolapse of the uterus, cystocele, rectocele, complete tear of the perineum; (xxi) inversion of the uterus, lateral and upward displacements; (xxii) bacteriology of the genital canal in health, physiology of the vagina at different ages; (xxiii) bacteriology of the genital canal in disease, puerperal infection, gonorrhœa; (xxiv) infection of the genital canal through the blood-stream, tuberculosis; (xxv) inflammation of the vulva and vagina; (xxvi) inflammation of the uterus; cervicitis, endometritis, metritis; (xxvii) inflammation of the fallopian tube and ovary, salpingitis and salpingo-oophoritis; (xxviii) inflammation of the pelvic cellular tissue, parametritis; (xxix) pregnancy in ovary, abdominal cavity, and fallopian tube; (xxx) new growths of vulva, urethra, and vagina; (xxxi-xxxii) fibroids of uterus; (xxxiii) polypi of uterus, elongation of the cervix; (xxxiv) sarcoma of uterus; (xxxv) carcinoma of uterus; (xxxvi) chorionepithelioma; (xxxvii) endometrioma and adenomyoma; (xxxviii) distension cysts of the ovary; (xxxix-xli) tumours of the ovary; (xlii) tumours of the tube and broad ligament; (xliii) development, defects of development, atresia; (xliv-xlvi) vaginal and vulvar operations; (xlvii) abdominal operations; (xlviii) minor gynaecological procedures, douching and tamponing, diathermy.

606/101

ROYAL COLLEGE OF SURGEONS OF ENGLAND

General Annual Report of the Council, 1944

published by the College, Lincoln's Inn Fields, London, W.C. 1, 1944. 28 pages.

This report records the work of all departments of the College during the year ended 31 July, 1944.

On 8 March, 1944, H.M. The King and H.R.H. The Duke of Gloucester visited the College. The Duke of Gloucester was admitted to the Honorary Fellowship of the College by the President, Sir Alfred Webb-Johnson.

Examinations. During the year 26 Fellows and 628 Members were admitted after passing the College examinations. The Council propose to seek power to grant the Fellowship to ophthalmological candidates who pass the primary examination and a special final examination equal in standard and similar in form to the ordinary examination but with subjects mainly ophthalmological.

Sir William H. Collins Chair of Pathology. Sir William Henry Collins has given £100,000 to the College for the endowment of the Department of Pathology and the institution of a chair of human and comparative pathology. Sir William has also arranged to bequeath a further £100,000 for the endowment of the Department of Anatomy and the institution of a chair of human and comparative anatomy. This is one of the greatest gifts ever bestowed on the College. In recognition of this and many other "liberal acts and distinguished labours eminently conducive to the improvement of natural knowledge and of the healing art," Sir William H. Collins was awarded the honorary medal of the College.

Library. Much of the library is still evacuated to the country but a small working library has been open to readers throughout the year. Accessions include 155 modern books and a number of historical items. Some additions have also been made to the list of current periodicals regularly received.

Lincoln's Inn Fields site. The College has acquired additional space in Lincoln's Inn Fields, and hopes that the Royal College of Physicians and the Royal College of Obstetricians and Gynaecologists will agree to come together in combined or adjacent buildings on this site.

White Paper on "A National Health Service". At a meeting of the Fellows of the College, held on 8 May, 1944, the White Paper was discussed. A brief account of the meeting is contained in the report.

The report records awards made, lectures and demonstrations given, and elections held during the year. The research work outlined in the report is given in greater detail in the College's Scientific Report, reviewed in *BMB* 606/102.

606/102

ROYAL COLLEGE OF SURGEONS OF ENGLAND

Scientific Report for the Year 1943-44

published by the College, Lincoln's Inn Fields, London, W.C. 1, 1944. 24 pages.

This report is divided into two sections dealing with (i) museum activities, and (ii) research.

Museum. During the year the museum staff have been principally occupied with the supervision of museum specimens at the various centres to which the collection was dispersed earlier in the war. No museum specimen has been damaged or destroyed from any cause during the period under review, and the Council of the College pay tribute to the authorities of the various institutions to

which material has been dispersed for their continued kindness in accommodating such material.

Donations included sets of old surgical instruments and a photograph of the outer coffin which enclosed Hunter's remains, taken after its discovery in the vaults of the church of St. Martin-in-the-Fields in 1859.

Additions to the museum comprised 286 specimens. Twenty-four demonstrations and lecture demonstrations were held in the museum and 14 papers on subjects connected with the museum were published.

Research has been confined to the *Bernhard Baron Research Laboratories*; no surgical research has been possible at the *Buckston Browne Research Farm* since 1940.

Progress is reported in the production of papain-trypsin digests of casein suitable for intravenous administration. In addition, the facilities of the laboratories have been placed at the disposal of the *Medical Research Council* for testing the products of various firms.

The series of experiments designed to test the effect of various sulphur-containing amino-acids on the incidence and severity of liver damage during arsenotherapy for syphilis has been extended, and results obtained have shown that with certain protective treatments the incidence of liver damage can be considerably reduced.

Four cases of acute carbon-tetrachloride poisoning were studied. In such cases acute liver necrosis is apparently the cause of death. One case recovered with methionine treatment; in another, where there was a combination of hepatic and renal dysfunction, methionine and chlorine were both employed, on the assumption that the renal dysfunction was related to choline deficiency.

The value of protein synthesis in hepatic disease has also been demonstrated. There are good reasons for believing that infective hepatitis adversely affects the synthesis of specific antibodies, and methionine and intravenous casein digests rich in methionine appeared to produce good results in infective hepatitis, homologous serum jaundice and severe burns.

Work on nerve regeneration after section and suture has produced valuable information on such diverse problems as the rate of degeneration and regeneration of axons of different sizes, and the relation between the state of the myelin sheath and the onset of function.

606/103

AIDS TO ORTHOPÆDIC SURGERY AND FRACTURES

by I. E. Zieve. Second edition. London, Baillière, Tindall and Cox, 1944. 270 pages. 6s. [£0.3]

This useful volume of the *Aids* series first appeared in 1929, written by E. Crook, of *Charing Cross Hospital*, London, and the new edition has been prepared by the surgical registrar of the same hospital. The book is a short survey of the subject, especially suitable for revision purposes. The greater part of the book is devoted to the locomotor system and deals with the effects of abnormal development, injury, inflammation and new growths; a chapter discusses the effects of these same influences on the nervous system, and a final chapter considers acquired deformities. There is obviously no space in a small book such as this for the full descriptions and numerous illustrations one expects in a text-book, but, in the limited space at his disposal, the author has succeeded in providing a great deal of information concisely written and well arranged. There is a good index.

Chapter headings: (i) congenital deformities; (ii) fractures; (iii) injuries to joints, muscles and tendons; (iv) inflammatory diseases of bones; (v) inflammatory diseases of joints, muscles, tendons and bursæ; (vi) new growths of bone; (vii) paralyses; (viii) acquired deformities.

606/104

TROPICAL MEDICINE

by Sir Leonard Rogers & Sir John W. D. Megaw. Fifth edition. London, J. & A. Churchill, 1944. 518 pages; 89 illustrations. £1 1s. [£1.05]

In the preface to the first edition of this book (1930) the authors wrote: "Considering the number of excellent books on Tropical Medicine which are on the market, the issue of this volume calls for an explanation." No explanation for the fifth edition is necessary, for in the intervening years the book has itself become one of those "excellent books". Both its authors have devoted their lives to the study of tropical disease, and their vast experience is reflected in the book, particularly in those sections dealing with diseases upon which they are recognized authorities.

The book is devoted chiefly to the recognition and management of the commoner diseases of warm climates; it contains only such details of microscopical technique as the general practitioner can carry out in his hospital or study. Special attention is paid to the geographical distribution of the more important diseases. Both authors have spent many years in India, and the diseases prevalent in that continent are given special consideration.

In the fifth edition, much has been rewritten, especially in the chapters on malaria, kala-azar, trypanosomiasis, the typhus fevers, leprosy, and the dietetic diseases. At the present time many additional military medical officers are serving in tropical and sub-tropical areas; many unfamiliar problems will face them, and this book should prove especially helpful to them. Interesting historical notes interspersed throughout the text prove the wide reading of the authors and tempt the historically-minded reader to refer to

the original accounts of important contributions to tropical medicine. Perhaps in a future edition, the writers will find space for a bibliography of the authorities cited. The book includes a number of good illustrations, and a full index is provided.

Chapter headings: (i) malaria, including blackwater fever; (ii) kala-azar; (iii) trypanosomiasis, sleeping sickness and Chagas' disease; (iv) relapsing fevers, rat-bite fever; (v) the leptospirosis group of diseases; (vi) yellow fever; (vii) the dengue group; (viii) the typhus fevers; (ix) plague; (x) undulant fever; (xi) amœbic dysentery; (xii) amœbic hepatitis and liver abscess; (xiii) bacillary dysentery; (xiv) cholera; (xv) hill diarrhoea and sprue; (xvi) leprosy; (xvii) yaws; (xviii) oriental sore; inguinal ulcerative granuloma; tropical ulcer; Madura foot; dermatomycosis; ainhum; chigger disease; lymphogranuloma or climatic bubo; (ix) ankylostomiasis; (xx) filariasis; (xxi) schistosomiasis; (xxii) snake poisons; (xxiii) dietetic errors in the tropics; (xxiv) dietetic diseases in the tropics; (xxv) climate as a disease factor; diseases caused by heat; diseases caused by light; (xxvi) the incidence of general diseases in the tropics; (xxvii) hints on the use of the microscope; (xxviii) general remarks; diagnosis of fevers; case-taking.

606/105

AFTER-TREATMENT

A Guide to General Practitioners, House-Officers, Ward Sisters and Dressers in the Care of Patients after Operation

by H. J. B. Atkins. Second edition. Oxford, Blackwell Scientific Publications, Ltd., 1944. 311 pages; 60 illustrations. 18s. [£0.9]

When the patient leaves the operating theatre his future welfare depends to a great extent on the kind of after-treatment he receives. This book is written for those who are called upon to undertake the post-operative care of patients. The author, who is assistant surgeon to Guy's Hospital, has interpreted "after-treatment" in its widest sense, to include the treatment necessary after such injuries as burns, concussion, contusion; post-operative diet, fluid administration; the control of vomiting; sleep; regulation of the bowels; the care of wounds. Details of the after-treatment of specific operations are dealt with on a regional basis. Particular attention is given to the problem of peritonitis, to the colostomy patient, and to the after-treatment of fractures. Highly specialized operations such as craniotomy for cerebral tumour, lobectomy, thoracoplasty and plastic operations are not included, as the author considers that after-treatment in these relatively new fields has not yet become standardized.

The first edition of the book appeared in 1942 and was well received; in this second edition new chapters on the post-operative treatment of children and on rehabilitation have been added, together with new sections on post-operative coronary thrombosis and the management of the diabetic patient in the post-operative period, and new material in the chapters in genito-urinary surgery and head injuries. The remainder of the text has received careful revision and additions have been made to the illustrations. This is an excellent book, of value to every member of the surgical team. There is a full index.

Chapter headings: (i) early post-operative treatment; (ii) operation wounds, scars and burns; (iii) the ear, nose and throat; (iv) the thyroid and breast; (v) the chest; (vi-viii) the abdomen; (ix) the genito-urinary system; (x) amputations and other operations on the limbs; (xi) fractures; (xii) the nervous system; (xiii) operations on children; (xiv) rehabilitation.

606/106

LONDON COUNTY COUNCIL

Interim Report of the County Medical Officer of Health and School Medical Officer for the year 1943. London, P. S. King & Staples, Ltd., 1944. 30 pages. 6d. [£0.025]

This report is presented by Sir Allen Daley, County Medical Officer of Health and School Medical Officer. Although a slender booklet compared with the pre-war reports, it contains sufficient information to prove the value of the work being carried out so devotedly by the medical staff of the London County Council during a most critical period in history.

During 1943 11 of the Council's hospitals were damaged as a result of enemy activity. From the beginning of the war to the end of 1943 there were 476 air-raid incidents at these hospitals and 141 patients, 86 hospital staff and 12 ambulance drivers lost their lives. At no time during this period was the reception of the sick and injured delayed and 700,000 patients were admitted to the Council's hospitals.

There was a substantial return of population to London during the year; there were more births (45,030) than in 1942 (40,654) and more deaths (39,322 as against 36,057).

The infant mortality-rate was 51 per 1,000 live births (57 in 1938 and 108 in 1918, the fourth year of the 1914-18 war). Maternal mortality (2.13 per 1,000 live births) showed a continued reduction on the figures for the two previous years (from 3.0 to 2.5).

Tuberculosis notifications numbered 5,848 (5,530 in 1942), but the number of deaths (2,460) was about the same. Steps are being taken by means of mass miniature radiography to diagnose the disease earlier. A radiography unit was acquired by the Council in 1943 and during October-December 13,334 miniature films were taken, and large films were considered advisable in 433 cases (3.2%); 25% of these showed pulmonary lesions.

The results of immunization against diphtheria are striking. During the year, 18,045 children were immunized and it is estimated that by July 1944 68% of London elementary-school

children had received protection. Diphtheria cases reported in the schools in 1943 were 562 compared with 3,576 in 1938.

There were 50 deaths from measles which at one time approached epidemic proportions. An influenza epidemic reached its peak in December, when 128 deaths were recorded in 1 week. Deaths from influenza for the whole of the year were 726, the highest since 1937 (198 in 1942).

Scarlet fever was more prevalent and virulent (11 deaths) but there were no notifications of smallpox or typhus fever.

There was a further increase in notifications of dysentery (mostly of a mild type) but deaths did not increase. Enteric fever, a disease spread mainly by the same channels as dysentery, reached a record low incidence of 47 cases, though the deaths numbered 10 (5 in 1942).

There were 205,577 admissions during 1943 to the Council's public health hospitals. 13,872 births (13,380 live births) took place in the Council's general hospitals and in addition 6,847 confinements at home were attended by the Council's own midwives.

The estimated number of elementary-school children in London in January 1943, was 231,634, and by the end of the year this number had increased to about 250,000, with a school attendance rate of nearly 77%. The results of routine medical inspections show that the condition of the children has, in several respects, improved compared with 1938. There is less verminous infestation and scabies, and there are fewer children with enlarged tonsils and adenoids than at the beginning of the war. The condition of the children's teeth is not quite so bad. The nutritional condition of the great majority of children in London still continues to be classed as satisfactory and the general opinion among the school doctors, nurses, teachers and care-committee workers was that there were no signs of any war-time physical or mental deterioration among London school children generally. About 77% of the children attending elementary schools received milk in the schools and about 31% had dinners in the schools.

The following comparisons are made in regard to the children examined in the four age groups in the two most recent war-time years, and those examined in the same age groups in 1938, the last complete pre-war year of medical inspection:

Numbers examined	1943	1942	1938
	96,902	88,325	169,995
Percentages			
Nutrition unsatisfactory	6.00	6.2	6.6
Nits or pediculi—hair	2.15	1.9	2.3
Teeth—obvious decay	31.01	36.0	29.8
Vision—6/9 or worse	22.61	23.8	32.2
Adenoids and enlarged tonsils	7.6	7.3	9.2
Skin diseases	1.8	2.0	1.0
Enlarged glands	1.2	1.2	1.5
External eye disease	1.9	1.9	1.7
Otorrhœa	0.5	0.4	0.6
Defective hearing	0.3	0.3	0.2
Heart disease	0.8	0.8	1.4
Anæmia	0.3	0.2	0.4
Lung disease (not T.B.)	1.3	1.1	1.5
Tuberculosis (pulmonary)	0.07	0.03	0.04
(other lesions)	0.10	0.05	0.02
Rickets (boys—entrants only)	1.4	1.1	1.0
(girls—entrants only)	0.9	0.8	0.4

With regard to the Council's mental health services, there was a continued fall in the number of mental patients, as was the case in the last war. Particulars given of the results of the work of placing in employment and industrial after-care of mentally defective boys and girls leaving the Council's special schools at sixteen years of age show that 10% of them will probably need care in an institution and that the other 90% may be expected to take their place, more or less successfully, in the community.

Over one-third of the members of the regular (peace-time) London Ambulance Service are now in the Armed Forces and their places have temporarily been taken by men and women mainly from the auxiliary service.

606/107

THE LISTER INSTITUTE OF PREVENTIVE MEDICINE

Report of the Governing Body, 1944. Published by the Lister Institute, Chelsea Bridge Road, London, S.W. 1. 1944. 15 pages.

The report of the Lister Institute for the year 1944 was presented by the Chairman of the Governing Body, Sir Henry Dale, at the annual meeting on June 19.

Some members of the staff are at present serving with the armed forces or dispersed to Oxford or Cambridge. During the year the Medical Research Council established a unit at the Institute for research into, and filtration of, blood plasma and serum for transfusion.

Bacteriological, immunological and serological studies Preliminary trials have been undertaken in the treatment of louse-borne typhus with anti-OX19 serum. Dr. A. Felix has been working on this serum from the horse, and a concentrated serum has been prepared at the Wellcome Physiological Research Laboratories. It is hoped to arrange for a strictly controlled clinical trial of the serum.

The typing of typhoid, paratyphoid and food-poisoning bacilli with the Vi bacteriophage has been continued and one hitherto unknown Vi-phage type of the typhoid bacillus was identified during the year as being responsible for a small outbreak of typhoid. This type does not seem to be indigenous to the British Isles. On the other hand, a Vi-phage type of *Bact. paratyphosum* B was found which must be considered indigenous to Britain.

Work has been carried out on dysentery prophylaxis, gas gangrene (including the methods of identification of clostridia), the nuclear structures of bacteria, hyaluronidase and hyaluronic acid.

Biochemical studies. Dr. W. T. J. Morgan and Mrs. R. van Heyningen have investigated pseudo-mucinous ovarian cyst fluids for the presence of the specific blood-group substances. The A substance has been isolated from ovarian-cyst fluid, and experiments have recently been started with the object of finding a method of preventing iso-immunization of the mother by the fetus, with resulting foetal death. Work has also been continued on the biochemical action of various bacterial toxins, notably *Cl. oedematis*, *Cl. welchii* and *Cl. septicum*.

Studies on gramicidin have been commenced by Dr. R. L. M. Syngé. These have for their object the relation of the chemical nature with the biological activities of this antibiotic.

Biophysical and physico-chemical studies have included work on the low-temperature drying of biological materials, on the large-scale processing of human serum and plasma for transfusion, on foetal and maternal haemoglobin, and on the osmotic pressure of foetal and "defatted" serum.

Vaccinia virus. Work on the cultivation of vaccinia virus on the chorio-allantoic membrane of the developing chick, suspended shortly after the outbreak of war, has now been resumed by Dr. D. McClean with a view to preparing sufficient quantities of suitable virus for field trials and for clinical use in vaccination.

Endocrinology. Dr. V. Korenchevsky has continued his studies on the effects of different combinations of hormones and vitamins on adult and senile rats.

Nutritional studies. The Ministry of Food has been anxious to ascertain more accurately the human requirement for vitamin A as derived from preformed vitamin A and from the provitamin carotene. This has been done by means of a human experiment carried out on volunteers at the Sorby Institute, Sheffield, by Miss E. M. Hume. Since July 1942 the volunteers have received a diet as deficient as possible in vitamin A and carotene. Observation was specially directed to the measurement of capacity for dark-adaptation and of plasma values for vitamin A and carotene. After about 15 months 2 subjects showed deterioration of the visual threshold, with slight skin symptoms and a very low vitamin-A plasma value. The experiment, which is still in progress, has indicated how large are the vitamin-A reserves in the liver of the healthy human subject.

The nutritive value of the nitrogenous substances of the potato has been investigated by Dr. H. Chick and the nitrogen of the potato has been found to have a biological value at least equal to that of the proteins of whole wheat, weight for weight.

A nutritional survey of women employed in Oxford factories and of local housewives of similar age and social position, carried out from the autumn of 1942 to the end of 1943, showed that the nutritional state deteriorated very slightly during that period, but more so among the factory workers than the housewives.

The capacity for synthesis of vitamin C by young apples on storage has been established by Dr. C. West and Dr. S. S. Zilva.

National Collection of Type Cultures. During the year over 4,000 cultures were distributed and some 200 strains were deposited for maintenance.

Many other investigations are recorded in this report.

607

GUIDE TO THE JOURNALS

Annals of Eugenics

12 : October 1944

- The families of the kings of Siam of the house of Chakri. (M. Smith) 151-157
- Genetic studies on ectopia lentis. II. Anthropometric and linkage data. (C. W. Cotterman & H. F. Falls) 158-168
- Allowance for double reduction in the calculation of genotype frequencies with polygenic inheritance. (R. A. Fisher) 169-171
- The estimation of map distances from recombination values. (D. D. Kosambi) 172-175
- The analysis of a tsetse-fly population. II. (C. H. N. Jackson) 176-205
- The inheritance of allelomorphs of the *Rh* gene in fifty-six families. (R. R. Race, G. L. Taylor, E. W. Ikin & A. M. Prior) 206-210

Archives of Disease in Childhood

19 : September 1944

- The treatment of coeliac disease with vitamin B complex and concentrated liver. (D. Paterson, M. Pierce & E. Peck) 99-110
- Atrophic sclerosis of the cerebral cortex associated with birth injury. (R. M. Norman) 111-121
- Prognosis and treatment of pneumonia in children. (F. L. K. Lewis) 122-125
- Observations on otitis media and mastoiditis in infancy. (E. C. R. Couper) 126-130
- Congenital atresia of the oesophagus : an attempt at surgical treatment. (J. N. O'Reilly, R. H. Franklin & M. D. Daley) 131-134
- Giant congenital diverticula and neonatal rupture of colon : a case associated with true congenital partial hypertrophy of the crossed type. (J. E. Morison) 135-137
- Imperforate anus : some observations regarding diagnosis of the level of obstruction. (A. W. Wilkinson) 138-139
- Allergic vomiting in an infant. (H. S. Brodribb) 140-142
- Two cases of pulmonary actinomycosis. (A. G. Watkins) 143-144

19 : December 1944

- Macrocytic anaemia in children : with a report of three cases showing megaloblastic erythropoiesis. (L. J. Davis) 147-154
- Refractory anaemia (Fancini type) : its incidence in three members of one family, with in one case a relationship to chronic haemolytic anaemia with nocturnal haemoglobinuria (Marchiafava-Micheli disease or 'nocturnal haemoglobinuria'). (J. V. Dacie & A. Gilpin) 155-162
- Erythroblastic anaemia with bone changes in Egyptian children ; possibly Cooley's type. (M. Diwani) 163-168
- Observations on the urine of the new-born infant. (J. Thomson) 169-177
- Myocarditis in acute infective diseases : a review of 200 cases. (C. Neubauer) 178-180

Biochemical Journal

38 : 1944

PARTIAL INDEX

- Chromatographic determination of Evans Blue in plasma and serum. (C. J. O. R. Morris) 203-204
- Isolation of trehalose from desert manna. (J. Leibowitz) 205-206
- The chemistry of wheat germ with particular reference to the scutellum. (J. J. C. Hinton) 214-217
- The metabolism of azo compounds. I. Azobenzene. (L. A. Elson & F. L. Warren) 217-220
- Changes in the skeleton during gestation and lactation in the rat. (G. M. Warnock & J. Duckworth) 220-224
- Qualitative analysis of proteins : a partition chromatographic method using paper. (R. Consden, A. H. Gordon & A. J. P. Martin) 224-232
- Studies on bacterial amino-acid decarboxylases. 1. *l* (+) -lysine decarboxylase. (E. F. Gale & H. M. R. Epps) 232-242
- Studies on bacterial amino-acid decarboxylases. 2. *l* (-) -tyrosine decarboxylase from *Streptococcus faecalis*. (H. M. R. Epps) 242-249
- Studies on bacterial amino-acid decarboxylases. 3. Distribution and preparation of codacarbonylase. (E. F. Gale & H. M. R. Epps) 250-256
- A liver storage test for the assessment of vitamin A. (K. Guggenheim & W. Koch) 256-260
- The biological value of carotene from various sources and the effect of vitamin E on the utilization of carotene and of vitamin A. (K. Guggenheim) 260-264
- The urinary elimination of nicotinamide methochloride by man. (P. Ellinger & R. A. Coulson) 265-270
- Investigations on the activity of the histaminase in normal and toxemic pregnancy. (R. Kapeller-Adler) 270-274

- A study of the determination of glucuronic acid by the naphthoresorcinol reaction, with the photoelectric absorptiometer. (S. W. F. Hanson, G. T. Mills & R. T. Williams) 274-279
- Carotene and lycopene in rose hips and other fruits. (F. C. Jacoby & F. Wokes) 279-282

38 : 1944

- Notes on the toxins of Egyptian scorpions. (A. H. Mohammed) 284-285
- Analysis of a partial hydrolysate of gramicidin by partition chromatography with starch. (R. L. M. Syngé) 285-294
- The esterases of skin. (R. H. S. Thompson & V. P. Whittaker) 295-299
- Bacterial tetrathionase : adaptation without demonstrable cell growth. (R. Knox & M. R. Pollock) 299-304
- Chromatographic investigation of the β -carotene content of serum of the newborn infant. (H. Hoch) 304-308
- The reaction between histidine and formaldehyde. (A. Neuberger) 309-314
- The microbiological assay of nicotinic acid in cereals and other products. (E. C. Barton-Wright) 314-319
- Mono-iodotyrosine. (C. R. Harrington & R. V. P. Rivers) 320-321
- The isolation of a Δ^4 -androstene-3 (β), 16, 17-triol from the urine of normal human males and females. (G. F. Marrian & G. C. Butler) 322-324
- On arginase and its participation in urea synthesis in the liver. (S. J. Bach, E. M. Crook & S. Williamson) 325-332
- The oxidative metabolism of *Ascaris suum*. (H. Laser) 333-338
- Studies on the metabolism of mould fungi. I. Phosphorus metabolism in moulds. (T. Mann) 339-345
- Studies on the metabolism of mould fungi. II. Isolation of pyrophosphate and metaphosphate from *Aspergillus niger*. (T. Mann) 345-351
- The effect of X-rays on the respiration of fowl erythrocytes. (L. Frankenthal & A. Back) 351-354

Brain

67 : June 1944

- The neurological complications of dissecting aortic aneurysm. (A. D. Weisman & R. D. Adams) 69-92
- A distinctive type of encephalomyelitis occurring among troops in the northern territory of Australia : a discussion of two fatal cases. (J. F. Horan, G. A. W. Johnston, J. H. Halliday, J. O'Brien & E. W. Hurst) 93-102
- A review of some recent observations on demyelination. (E. W. Hurst) 103-124
- Fibre interaction in injured or compressed region of nerve. (R. Granit, L. Leksell & C. R. Skoglund) 125-140

British Dental Journal

76 : 7/1/44

- Ulcerative stomatitis in a case of subacute monocytic leukaemia. (B. Boyd-Cooper) 1-4
- Amalgam restorations in fissural cavities in posterior teeth. (G. E. M. Hallett) 4-7
- The alginates in dentistry. (E. Matthews) 8-9

76 : 21/1/44

- Fluorosis and dental caries on Tyneside. (R. Weaver) 29-40

76 : 4/2/44

- Growth at the mandibular condyle in relation to some deformities. (M. A. Rushton) 57-68
- A fundamental issue. (N. G. Bennett) 68-69

76 : 18/2/44

- Acute ulcerative gingivitis : the prevention of relapse. (R. J. Eustace) 83-86
- The dentist and the law. (D. M. Paterson) 87-91
- Surface pitting on an acrylic resin denture. (J. Osborne) 91-92
- A dental centre. (G. H. V. Froggatt) 93

76 : 3/3/44

- Nutritional deficiencies and dental caries in northern India. (C. D. M. Day) 115-123
- The role of the dental hygienist. (J. W. Smith) 123-125

76 : 17/3/44

- Nutritional deficiencies and dental caries in Northern India. (C. D. M. Day) 143-147
- Vincent's infection : observations and conclusions regarding the aetiology and treatment of 1,017 civilian cases. (A. F. Summers) 147-155

76 : 6/4/44

Vincent's infection: observations and conclusions regarding the aetiology and treatment of 1,017 civilian cases. (A. F. Stammers) 171-177
Precautions in the dental treatment of tuberculosis patients. (D. B. Cruickshank) 178-179
Angioneurotic oedema. (L. Lakner) 179-181
A review of two hundred and fifteen fractures of the maxillae. (J. W. Hallam) 181-182

76 : 21/4/44

Acute infections around erupting mandibular third molar teeth. (A. E. Perkins) 199-204
Vincent's infection: observations and conclusions regarding the aetiology and treatment of 1,017 civilian cases. (A. F. Stammers) 205-209

76 : 5/5/44

The pathogenesis of dental caries. (P. Pincus) 231-239
A simplified method of treatment for maxillary fractures. (A. B. MacGregor) 239-241

76 : 19/5/44

A new approach to full denture construction. (E. Matthews) 261-268
Sulphonamides in dentistry. (O. F. Brown) 269-271
A case of ulcerative gingivitis. (G. H. English) 271-272
Some wartime experiences of a dental officer. (H. S. Golding) 273-276

76 : 2/6/44

School dentistry in rural areas. (H. D. Hall) 295-297
Emergency silver amalgam and stainless steel crown. (R. G. M. Heavenor) 297-300
The anodic treatment of aluminium and its alloys for use in the mouth. (G. G. T. Tregarthen) 300-301

76 : 16/6/44

Modern phosphorus caries and necrosis. (R. Kennon & J. W. Hallam) 321-330
Prophylaxis for phosphorus workers. (R. Baron) 331-332
Rapidly adapted connecting bars and locks for metal or acrylic splints. (H. N. Toomey) 332-337

77 : 7/7/44

Progress in acrylic conservative technique—an evaluation of its present scope. (R. Cutler) 1-10
Ampoule feed tube for di-vinyl ether. (A. R. Brown) 10-12

77 : 21/7/44

State dental service. (G. F. Charles) 29-36
The use of acrylic resin for facial prostheses. (F. Coffin) 36-39
The trend of plastics in dentistry and surgery. (S. A. Leader) 39-40

77 : 4/8/44

The acidity of dental cements. (W. Harvey, L. F. Le Brocq & L. Rakowski) 61-69
Electro-forming and its application in dentistry. (E. M. Natt) 69-73
Oral hygiene: its application in the treatment of acute ulcerative gingivitis. (G. H. Leatherman) 73-75
The palatal injection. (J. Angelman) 75-76

77 : 18/4/44

The acidity of dental cements. (W. Harvey, L. F. Le Brocq & L. Rakowski) 89-99
"Dens in dente." (B. Boyd-Cooper) 99-101

77 : 1/9/44

Dental education—the problem of staffing schools. (F. C. Wilkinson) 121-126
Some clinical, histological and biological observations on the acidity of dental cements. (E. B. Manley) 126-129
A composite odontome at a very early age. (S. A. Riddett) 129-131

77 : 15/9/44

The inferior alveolar injection for fillings. (C. N. Jeffries) 153-159
Sarcoidosis or tuberculosis?: clinical history and treatment. (J. Campbell) 159-160
Sarcoidosis or tuberculosis?: histology, diagnosis and discussion. (T. T. Read) 160-163

77 : 6/10/44

Fluorine and dental caries: further investigations on Tyneside and in Sunderland. (R. Weaver) 185-193
Maxillo-facial casualties from France. 194-195

77 : 20/10/44

Experimental investigations of parodontal disease: 1. The significance of the blood supply in gingival health and disease of the ferret. (J. D. King) 213-221

77 : 3/11/44

Experimental investigations of parodontal disease: 1. The significance of the blood supply in gingival health and disease of the ferret. (J. D. King) 245-254

77 : 17/11/44

The probable age-change in incisor dentine. (M. A. Rushton) 277-279
Silver amalgam-stainless steel bridges: indirect precision technique. (R. G. M. Heavenor) 279-283

77 : 1/12/44

The moulding of acrylic teeth in the laboratory. (A. G. Attenborough) 311-315

77 : 15/12/44

Benign bone-forming tumours of the jaws. (F. C. Wilkinson & E. Pollak) 341-346
This quaint profession. (G. E. M. Hallett) 347-349

British Journal of Dermatology and Syphilis

56 : September-October 1944

A case of light sensitization. (D. Erskine) 195-198
Some observations on skin diseases with the Army in India. (A. Bigham) 199-202

56 : November-December 1944

The phenol-camphor treatment of dermatophytosis. (B. Phillips) 219-227
Angiokeratoma. (E. L. Cohen) 228-230

British Journal of Experimental Pathology

25 : August 1944

Erythrocytes in cytoplasm and nuclei of liver cells. (A. Rosin & L. Doljanski) 111-115
Influence of milk factor on the incidence of breast cancer induced by oestrone. (I. Dmochowski & W. E. Gye) 115-118

Transmission of the mammary tumour inciting factor by splenic grafting. (I. Dmochowski) 119-120
Stability of fibrinogen in normal and pathological plasma. (E. Wertheimer, B. Shapiro & I. Fodor-Salomonowicz) 121-125
The effects of prolonged administration of small doses of alloxan upon the islet tissue of the rat pancreas. (H. Hughes & G. E. Hughes) 126-130
Influenza virus as a laboratory contaminant. (C. H. Andrewes, R. E. Glover, F. Himmelweit & W. Smith) 130-134

25 : October 1944

Investigation into the production of bacteriostatic substances by fungi. Preliminary examination of a fourth 100 species, all penicillia. (H. Wilkins & G. C. M. Harris) 135-137
Mammary tumour inducing factor and genetic constitution. (I. Dmochowski) 138-140
Infection of mice with *Mycobact. tuberculosis* (bovis) by the respiratory route. (R. E. Glover) 141-149
Magnesium potentiation of adenosine triphosphate shock and other shock-inducing measures. (H. N. Green & H. B. Stoner) 150-159
Muscular fatigue in the albino rat, and its relationship to the thyroid. (J. L. Malcolm & V. I. E. Whitehead) 160-163
The nucleic acid and nucleotide content of tumours. (J. N. Davidson & C. Waymouth) 164-173
Sensitization to "Tetryl." (P. G. H. Gell) 174-192

British Journal of Ophthalmology

28 : November 1944

Unilateral and bilateral retinoblastoma. A possible histological difference. (J. N. Cumings & A. Sorsby) 533-537
Observations on the transparency of the conjunctiva. (P. A. Gardiner) 538-554
Photographs of retinal detachment in aphakia before and after operation. (E. Rosen) 554-556
Studies in dark adaptation as a means of detecting deficiency of vitamin "A." (G. W. Robertson & J. Yudkin) 556-568
Snake venom ophthalmia. (H. Ridley) 568-572
Plastic spheres for implantation into Tenon's capsule in the Frost-Lang type operation for enucleation of the eyeball. (R. E. Wright) 573-574
The local application of penicillin solution to the eye. (R. E. Wright) 574-575
The end results of operation for detachment of the retina. (With a follow up of fifty successful cases.) (M. L. Hine) 575-585

28 : December 1944

Retinal micro-aneurysms and punctate haemorrhages. (A. J. Ballantyne & A. Loewenstein) 593-598
A simple method of demonstrating nystagmus in certain miners. (A. C. Reid) 598-599
An introduction to Bishop Berkeley's theory of vision. (M. Murray) 600-611
The effect of the duration of stimulus on threshold measurements in the dark adapted eye. (S. Yudkin) 611-617
Bilateral partial ectasia of the nerve head with peripapillary ectasia. (I. S. Macgregor) 618-622
The dionine effect in the conjunctiva. (A. Loewenstein) 622-625
Buried silk, catgut and strabismus sutures. (J. Foster) 625-629
Photometer for measuring the scotopic candle-powers of self-luminous ophthalmic test objects. (W. S. Stiles) 629-637

British Journal of Radiology

17 : November 1944

Stress fractures of the first rib. (B. R. Alderson) 323-326
Dosage-rate in radiotherapy: symposium. (L. H. Gray, F. Ellis, G. C. Fairchild & E. Paterson) 327-342
Observations on opaque myelography of lumbar disc herniations. (D. C. Eaglesham) 343-348
The action of neutrons on bacteria. (F. G. Spear) 348-351
Stellate translucencies as a sign of gall-stones. (A. S. Johnstone) 352-353

17 : December 1944

Further observations on lung disease in boiler-scalers. (L. Dunner & R. Hermon) 355-358
Energy absorption. III. The mathematical theory of integral dose and its applications in practice. (W. V. Mayneord) 359-367
Serial roentgenograms of the chest in periarteritis nodosa as an aid to diagnosis. (A. Elkeles) 368-373
The action of neutrons on the developing rat retina. (F. G. Spear & K. Tansley) 374-379
A case of bronchial carcinoma presenting diagnostic difficulties. (R. B. Guyer) 380-382
An unusual case of joint disease. A possible example of arthritis psoriatica. (H. Jungmann & V. S. Stern) 383-385
Cystic disease in an azygos lobe, with phrenic nerve paresis. (G. F. Rees-Jones) 386

British Journal of Surgery

32 : October 1944

The early history of syphilis. (J. J. Abraham) 225-237
Some experience of reparative surgery in the Middle East: with a short review of 1,200 cases treated during the last two years. (M. C. Oldfield) 237-246
Second thoughts on the abdominal surgery of "total" war—a review of over 1,300 cases. (G. Gordon-Taylor) 247-258
Ischemic nerve lesions occurring in Volkmann's contracture. (W. Holmes, W. B. Hight & H. J. Seddon) 259-275
Surgery in an airborne division. (C. J. Longland & L. Kessel) 275-281
The clinical value of a growth-promoting substance in the treatment of indolent wounds. (A. B. Kerr & H. Werner) 281-287
Fractures of the zygomatic tripod. (H. G. Ungley & S. C. Suggit) 287-299
Rupture of the pancreas. (G. Keynes) 300-303
A gastroscopic control of the treatment of gastric ulcer by duodenal feeding. (H. Freeman) 303-308
Carotid ligation for intracranial aneurysm. Report of a case studied by electroencephalography. (L. Rogers) 309-311
Fascial slinging of the scapula and clavicle for dropped shoulder and winged scapula. (G. C. Dorling) 311-315
Malignant transformation in a previously benign tubular adenoma of the kidney. (W. Buckley) 315-319
Congenital cyst of the common bile-duct containing stones and undergoing cancerous change. (S. T. Irwin & J. E. Morison) 319-321

British Journal of Tuberculosis and Diseases of the Chest

38 : October 1944

"What is the right time, please?" A surgeon's answer. Presidential address to the Tuberculosis Association, 1944. (J. E. H. Roberts) 105-111
Carbon dioxide by inhalation in the management of cough. (A. L. Banyai & A. V. Cadden) 111-116
Mass miniature radiography in the Royal Air Force. (R. R. Trail, H. J. Trenchard, C. E. H. Anson, L. G. Scott, F. T. Clive, A. C. Evans, J. A. Kennedy, J. W. Pierce, C. F. Price & H. A. Warner) 116-140

British Journal of Venereal Diseases

20 : December 1944

Penicillin. (Editorial) 131-132
Penicillin in venereal diseases—1. (A. Fleming) 133-136

Penicillin in venereal diseases—2. (J. Suchet) 136-140
 Extra-urethral cases in an African venereal diseases hospital. (W. A. Young) 141-154
 The intensive therapy of early syphilis. (D. M. Pillsbury, C. J. Courville, R. H. Crede, J. D. Myers & C. R. Wise) 154-165

British Medical Journal

2: 21/10/44

Plasma volume in traumatic shock. (A. C. Crooke, C. J. O. R. Morris & R. G. Bowler) 521-522
 Eustachian obstruction and otitic barotrauma in air-crews of heavy bombers. (R. M. S. Matthews) 523-525
 A laboratory test for diagnosis of smallpox. (C. E. van Rooyen & R. S. Illingworth) 526-529
 Air embolism as a complication of vaginal douching in pregnancy. (G. Forbes) 529-531
 Active convalescence of hernial repairs. (D. J. Martin) 531-532

2: 28/10/44

The need for asepsis in local penicillin therapy. (W. McKissock, V. Logue & I. Bartholomew) 551-555
 Some mistaken diagnoses in the common infectious fevers. (D. F. Johnstone) 555-559
 Gastro-intestinal bleeding due to vitamin K deficiency complicating labour. (E. Malone) 559-560
 Spontaneous rupture of an apparently normal spleen. (L. E. Jones) 561-562
 Pneumoperitoneum. (D. Leys) 562-563

2: 4/11/44

Infective hepatitis in the garrison of Malta. (K. Damodaran & S. J. Hartfall) 587-590
 Human-milk intoxication due to B. avitaminosis. (L. Fehily) 590-592
 Acute brachial radiculitis. (J. W. A. Turner) 592-594
 The transnasal intragastric Ryle's tube in tropical practice: a life-saving measure. (G. A. Ransome, L. M. Gupta & J. C. S. Paterson) 594-596
 Suprarenal haemorrhage: report of a case. (C. J. Williams & R. Ellis) 596-597

2: 11/11/44

Acute perforated peptic ulcer: frequency and incidence in the west of Scotland. (C. F. W. Illingworth, L. D. W. Scott & R. A. Jamieson) 617-620
 Epistiotomy. (J. D. S. Flew) 620-623
 Rapid replacement of fluid in haemorrhage and shock. (J. D. P. Graham) 623-625
 Underwater blast injuries of the abdomen. (T. Moore) 626-627
 Toxic reactions after administration of paraldehyde. (R. E. Hemphill & H. Heller) 628-629
 Apparatus for systemic administration of penicillin to young children. (C. A. St. Hill) 631
 Post-war rehabilitation and resettlement. (G. D. Kersley) 632

2: 18/11/44

Studies on hepatic dysfunction. II. The value of sulphur-containing amino-acids and casein digest in the prevention of post-arsphenamine jaundice. (J. Beattie & J. Marshall) 651-655
 Acute perforated peptic ulcer: frequency and incidence in the west of Scotland. (C. F. W. Illingworth, L. D. W. Scott & R. A. Jamieson) 655-658
 Experiences with the giant magnet and metallic intraocular foreign bodies in recent battle casualties. (R. E. Wright & H. A. G. Duncan) 658-659
 Latent mastoiditis in infancy? (W. H. Patterson & G. S. Smith) 659-661
 Secondary abdominal pregnancy. (F. E. Stock) 661-662
 Mepacrine for malaria. (Medical Research Council Committee on Malaria) 664
 The portraits of William Harvey. (G. Keynes) 669-670

2: 25/11/44

General anaesthesia in shock. (A. C. Crooke, C. J. O. R. Morris & R. G. Bowler) 683-686
 The use of penicillin pastilles in oral infections: a preliminary report. (A. B. MacGregor & D. A. Long) 686-689
 An analysis of 259 of the recent flying-bomb casualties. (R. C. Bell) 689-692
 Massive surgical emphysema during the course of general anaesthesia. (N. R. Barrett & D. Thomas) 692-693
 An unusual case of generalized tuberculosis. (W. H. Mylechreest & I. M. Scott) 693-694

2: 2/12/44

"Growth" and the diabetogenic action of anterior pituitary preparations. II. Growth and experimental insulin-insensitive diabetes. (F. G. Young) 715-718
 The action of penicillin on leptospira and on leptospiral infections in guinea-pigs. (J. M. Alston & J. C. Broom) 718-719
 A case of Weil's disease treated with penicillin. (V. L. Hart) 720
 Amebiasis: some difficulties of diagnosis. (C. N. Morgan) 721-722
 An investigation into the use of sulphasuxidine in operations on the rectum and colon. (D. H. Mackenzie) 722-723
 A smallpox epidemic. (T. St. M. Norris) 724-725

2: 9/12/44

Treatment of hyperthyroidism with thiouracil. (A. M. Nussey) 745-748
 The haemoglobin level in municipal-school children: effect of iron therapy, school dinners, and season. (R. H. Dobbs, H. M. M. Mackay & K. Bingham) 748-751
 The dietary control of alloxan diabetes in rats. (J. H. Burn, T. H. C. Lewis & F. D. Kelsey) 752-754
 Antibacterial action of 2-aminophenol (O-aminophenol). (M. Barber & G. A. D. Haslewood) 754-755
 Mediastinal teratoma successfully removed by operation. (A. W. Fawcett) 755-756
 The incomplete antibody in Rh immunization. (R. R. Race & G. L. Taylor) 756
 Preamble to post-war food education. (F. Le Gros Clark) 763-765

2: 16/12/44

Smallpox vaccination by the multiple-pressure method. (H. J. Parish) 781-784
 A two-stage method of treatment in diabetes. (R. H. Hicks) 784-786
 Some aspects of gonorrhoea in the Navy. (S. Matthews & F. G. Beilby) 787-788
 Treatment of wounds by delayed suture. (W. Patrick) 788-790
 The origin of bronchogenic tuberculosis in the adult: pathological aspects of "exogenous and endogenous reinfection." (W. Pagel) 791

2: 23/12/44

The supply of bodies for dissection: a historical review. (N. M. Goodman) 807-811
 Estimation of heat radiation in clinical practice. (D. S. Evans & K. Mendelsohn) 811-814
 Radical operation for varicose veins. (H. Dodd) 814-816
 Sulphonamide allergy: the persistence of desensitization. (R. G. Park) 816-817
 Penicillin in civilian practice. (H. B. May) 817-818
 Observations on scabies at the St. Pancras bathing centre. (M. W. Giffen) 825

2: 30/12/44

The aetiology of erythema nodosum. (C. B. Perry) 843-847
 Studies on hepatic dysfunction. III. Carbon tetrachloride poisoning: sulphur metabolism. (J. Beattie, P. H. Herbert, C. Wechtel & C. W. Steele) 847-849
 A critique of gastroscopy. (N. C. Tanner) 849-851
 Bismuth therapy in jaundice during antisyphilitic treatment. (J. R. Forbes) 852
 Severe abdominal crush injury: a study of the mechanics in an extreme case. (D. H. Lees) 853-854

Clinical Science

5: 1944

A simple standard procedure for obtaining blood having a haemoglobin content identical with arterial blood. (E. B. Reeve & N. A. Neville) 1-3
 Observations upon a vascular axon reflex: a correction. (T. Lewis) 5-7
 Effects of supercooling skin. (T. Lewis) 9-15
 Ophthalmoplegia in Graves' disease. (F. F. Rundle & C. W. Wilson) 17-29
 Bulging of the eyelids with exophthalmos. (F. F. Rundle & C. W. Wilson) 31-49
 The orbital tissues in thyrotoxicosis: a quantitative analysis relating to exophthalmos. (F. F. Rundle & E. H. Pochin) 51-74
 Exophthalmos in guinea pigs injected with pituitary extracts. (E. E. Pochin) 75-91
 Massive hepatic necrosis and diffuse hepatic fibrosis (acute yellow atrophy and portal cirrhosis): their production by means of diet. (H. P. Himsworth & L. E. Glynn) 93-123
 Cardiac output in severe anaemia. (R. P. Sharpey-Schafer) 125-132
 The prevention of experimental massive hepatic necrosis by methionine. (H. P. Himsworth & L. E. Glynn) 133-137

Dental Record

64: January 1944

The early extraction of the first permanent molar as the best method of preserving the dentition as a whole. (A. A. Wilkinson) 1-8
 Natural improvement in incisor alignment. (O. N. Catchpole) 8
 An unsuccessful attempt to move "depressed" deciduous molars. (H. C. Visick) 9-11

64: February 1944

The early extraction of the first permanent molar as the best method of preserving the dentition as a whole. (A. A. Wilkinson) 25-35
 A comparison between the clinical and radiographic depth of dental caries. (J. C. Robertson) 35-36
 Plates worn at night only. (W. T. Johnson) 37-39
 Osteoarthritis. (M. B. Ray) 39-40

64: March 1944

The early extraction of the first permanent molar as the best method of preserving the dentition as a whole. (A. A. Wilkinson) 51-58
 The distribution of the enamel cuticle and its significance. (A. I. Darling) 58-62

64: April 1944

Pulp reactions to dental cements. (E. B. Manley) 75-86
 A cure of thumb-sucking with marked changes in occlusion. (K. C. Smyth) 86-87
 Problems of medical relief in the immediate post-war phases. (M. D. MacKenzie) 88-89

64: May 1944

Amalgam protected cement fillings for approximal cavities in posterior teeth. (C. Levy) 99-102
 Mottled enamel, M-hypoplasia and dental caries. (J. D. King) 102-110

64: June 1944

The colloidal concept of disease: with special reference to dentistry. (F. W. Broderick) 123-126
 Localised vertical growth disturbance. (P. G. Capon) 127-132
 Beveridge—and the future of orthodontics. (R. Cutler) 132-140

64: July 1944

The colloidal concept of disease: with special reference to dentistry. (F. W. Broderick) 147-150
 Simplified production of models for full dentures. (H. Hirsckorn) 151-157
 Primary chancre of the lips. (T. T. Read) 158-159
 Ethyl chloride and cavity preparation. (J. Button) 161-162
 Diet as it concerns the teeth and gums. (E. Sprawson) 162

64: August 1944

The colloidal concept of disease: with special reference to dentistry. (F. W. Broderick) 171-174
 Some practical aspects of thumb sucking. (T. J. Wood) 174-178
 The care of the teeth in industry. (G. L. Roberts) 179-185

64: September 1944

The colloidal concept of disease: with special reference to dentistry. (F. W. Broderick) 195-198
 Some aspects of dentistry in relation to aviation. (W. Harvey) 199-209

64: October 1944

The colloidal concept of disease: with special reference to dentistry. (F. W. Broderick) 219-222
 The root-granuloma, dental or radicular, and dentigerous or follicular cysts. (R. Fairhurst) 223-233

64: November 1944

The colloidal concept of disease: with special reference to dentistry. (F. W. Broderick) 243-248
 The root-granuloma, dental or radicular, and dentigerous or follicular cysts. (R. Fairhurst) 249-256

64: December 1944

The colloidal concept of disease: with special reference to dentistry. (F. W. Broderick) 267-271
 Health and the student. (G. V. Watt) 272-276
 The surgical retention of full dentures. (L. Lakner) 277-280

Edinburgh Medical Journal

51: July-August 1944

The administration of drugs. (J. H. Gaddum) 305-319
 Bacterium enteritidis septicaemia. (S. McDonald) 320-326
 Nitrogen balance in chronic kidney disease. (O. Olbrich) 327-334
 The effect of surgical operation upon capillary resistance. (H. Scarb. oeph) 335-338
 The prophylaxis of cutaneous cancer. (R. Aitken) 339-345

51: September 1944

The chemistry of cell nuclei. (E. Stedman) 353-366
 Rehabilitation in the army. (J. J. R. Dunlop) 367-370
 Vitamin P. Observation on the capillary resistance in two cases of scurvy. (H. Scarborough) 381-387
 Propylene glycol vapour as an air disinfectant. II. (J. P. Duguid & S. W. Challinor) 388-395

51 : October 1944

- Collapse therapy: the planning of policy in certain cases. (R. Y. Keers & B. G. Rigden) 401-416
Obstetrical responsibility in the prevention of foetal and neonatal deaths. (J. Sturrock) 417-429
Nutrition and diet in war-time. (L. S. P. Davidson) 430-438
A case of dyshaemopoietic anaemia with megaloblastic marrow and normocytic blood picture responding to liver therapy. (A. J. Rhodes) 439-443

Glasgow Medical Journal

142 : July 1944

- Antenatal diet and its influence on still-births and prematurity. (C. S. Cameron & S. Graham) 1-7

142 : August 1944

- Plasma phosphatase and bone disease. (N. Morris) 31-39
A case of intersexuality (pseudhermaphroditism). (A. Sharman) 40-44

142 : September 1944

- A study of vitamin C saturation in hospital children. (D. H. Wallace & P. Adler-Tanz) 55-64

142 : October 1944

- Transplantation of the ureters into the bowel. (A. Jacobs) 97-106
Recovery in a case of staphylococcal meningitis treated by chemotherapy. (D. Brash) 107-110

142 : November 1944

- The significance of the Rh factor in medicine and obstetrics. (D. F. Cappell) 125-155
A case of accessory pancreas in an unusual position complicated by acute necrosis. (H. B. Young) 156-164

142 : December 1944

- Peptic ulcer: a study of the number of cases treated in the Western Infirmary of Glasgow during 46 years (1897 to 1942). (J. Carslaw) 183-188
The tuberculin patch test. (M. D. Giles) 189-194
Systemic changes in blood vessels and connective tissues and acute necrosis of the pancreas. (W. N. Rogers) 195-203

Guy's Hospital Reports

93 : 1944

- Measles. (R. E. Smith) 8-58
A fatal case of skin diphtheria. (H. R. S. Harley & M. Zia-Ullah) 59-61
A note on secondary diphtheritic infection of empyema and thoracotomy wounds. (R. C. Brock) 62-66

Journal of Anatomy

78 : January 1944

- Phases of maturation and fertilization in human ova. (W. J. Hamilton) 1-4
Transuterine ('internal') migration of the ovum in sheep and other mammals. (J. D. Boyd, W. J. Hamilton & J. Hammond) 5-14
The re-innervation of muscle after various periods of atrophy. (E. Gutmann & J. Z. Young) 15-43
The mechanism of rotation at the first carpo-metacarpal joint. (R. W. Haines) 44-46
The anatomical basis of cortico-striate connexions. (P. Glees) 47-51
Experimental studies on the development of the pronephric duct in anuran embryos. (Ti-Chow Tung & Su-Hwei Ku) 52-57

78 : April 1944

- An experimental study of optic connexions in the sheep. (O. E. Nichterlein & F. Goldby) 59-67
Observations on the volume, viscosity and nitrogen content of synovial fluid, with a note on the histological appearance of the synovial membrane. (D. V. Davies) 68-78
Histogenesis of pituitary cells in the chick. (W. M. Shanklin) 79-93
Observations on the development of the human vertebral column. (G. M. Wyburn) 94-102
The surface area of the intestinal mucosa in the rat and in the cat. (H. O. Wood) 103-105
The patellar index in mammals. (H. Haxton) 106-107

78 : July 1944

- The lymphocyte content of rabbit bone marrow. (J. M. Yoffey & J. Parnell) 109-112
The contribution of the medial fillet and stria-hypothalamic fibres to the dorsal supra-optic decussation, with a note on the determination of the lateral fillet. (P. Glees) 113-117
Observations on the histology of the cholechocho-duodenal junction and papilla duodeni, with particular reference to the ampulla of Vater and sphincter of Oddi. (J. Kirk) 118-120
The effect of 1:2:5:6-dibenzanthracene on the lymph-nodes of the rat. (A. Lasnitski & D. L. Woodhouse) 121-129
Post-natal growth changes in the human prostate. (G. I. M. Swyer) 130-145
The effect of oestrogenic stimulation on the mangabey prostate. (F. M. P. Eckstein & S. Zuckerman) 146
Unusually long pregnancy in a macaque. (F. M. P. Eckstein) 147
The inguinal canal in the foetus and new-born. (H. Curl & R. G. Tromly) 148-149

78 : October 1944

- A study of the Bantu female pelvis. (O. S. Heyns) 151-166
The evolution and functional significance of the transverse carpal arch of man. (H. Hughes) 167-172
The use of an agar gel in the sectioning of mammalian eggs. (D. M. Samuel) 173-175
The behaviour and fate of skin autografts and skin homografts in rabbits. A report to the War Wounds Committee of the Medical Research Council. (P. B. Medawar) 176-199
The cranial capacity of the living, calculated automatically by a nomographical instrument. (G. F. Hamilton) 200-203

Journal of Hygiene

43 : September 1944

- Studies in the dynamics of disinfection. II. The calculation of the concentration exponent for phenol at 35° C. with *Bact. coli* as test organism. (R. C. Jordan & S. E. Jacobs) 363-369
Some bacteriological aspects of dehydrated foods. (R. B. Haines & E. M. L. Elliot) 370-381
Germicidal mists and vapours in air disinfection. (A. H. Baker & C. C. Twort) 382-394
Factor analysis as an aid to nutritional assessment. (W. H. Hammond) 395-399
Some epithelial changes in fluorosis. (L. Spira) 400-401
Incidence of dystrophies caused by fluorine in organs regulated by the parathyroid glands. (L. Spira) 402-408
The application of the principle of partial pressure of gases to Haldane's method of stage decompression. (G. W. M. Boycott) 409-410
The typing of strains of *Bact. paratyphorum* B by the biochemical method of Kristensen and Bjölen. (J. Macnaughtan) 411-412

- Cytological observations on *Bact. coli*, *Proteus vulgaris* and various aerobic spore-forming bacteria with special reference to the nuclear structures. (C. F. Robinow) 413-423
The bacteriology of activated sludge. (L. A. Allen) 424-431

Journal of Laryngology and Otology

59 : February 1944

- New otological views. (A. Schwarzbart) 47-61
A case of sarcoma of the ethmoid. (W. M. Mollison) 62
The audiometric dip. (W. S. Adams) 63-64

59 : March 1944

- The treatment of chronic suppurative otitis media by the local application of penicillin and other drugs. (E. G. Collins & K. E. A. Hughes) 81-95
The use of amnioplastin in the surgery of the ear. (M. Sugar) 96-100
An auto-anæsthetic apparatus suitable for ear, nose and throat work. (T. B. Jobson) 101

59 : April 1944

- The conservative treatment of chronic suppurative otitis media in adults. (T. M. Banham & E. D. D. Dickson) 117-135
Gastro-enteritis and mastoiditis in infants. (B. Cohen) 136-145
Meningitis following mastoid infection by *Bacillus proteus*. (M. Sugar) 146-150
Postural instillation: an added note. (A. J. Moffett) 151-153

Journal of Mental Science

90 : July 1944

- A study of the histology of the testis in schizophrenia and other mental disorders. (R. E. Hemphill, M. Reiss & A. L. Taylor) 681-695
The significance of atrophy of the testis in schizophrenia. (R. E. Hemphill) 696-709
A psychometric method of determining intellectual loss following head injury. (W. R. Reynell) 710-719
Mental tests in senile dementia. (H. Halstead) 720-726
Psychiatric states in 130 ex-service patients. (H. Stalker) 727-738
Resort to phantasy in individuals and societies. (G. R. Peberdy) 739-745
Foreign service neurosis. (J. F. Burdon) 746-752
Loss of spatial orientation, constructional apraxia and Gerstmann's syndrome. (E. Stengel) 753-760
Acute confusional insanity and delirium. (E. S. Stern) 761-766
Insulin treatment in neurosis. (D. E. Sands) 767-771
A study of acute neurotic depression as seen in military psychiatry and its differential diagnosis from the depressive psychoses. (G. T. T. Stockings) 772-776
Prolonged memory defects following electro-therapy. (M. B. Brody) 777-779
Shock therapy in the presence of physical contra-indications. (M. Straker) 780-783
Non-obstructive unilateral hydrocephalus. (A. Roberts) 784

90 : October 1944

- Crime, senescence and senility. (W. N. East) 835-850
Types of personality: a factorial study of seven hundred neurotics. (H. J. Eysenck) 851-861
Neuroses in native African troops. (L. A. Nichols) 862-868
The neurotic dyspeptic soldier. (S. D. Mitchell & C. S. Mullin) 869-874
Death from electrical convulsion therapy. (F. J. Napier) 875-878

Journal of Obstetrics and Gynaecology of the British Empire

51 : October 1944

- Intra-epidermal carcinoma (Bowen's Disease) of the vulva: a report on two cases. (T. N. A. Jeffcoate, T. B. Davie & C. V. Harrison) 377-385
The control of *Staphylococcus aureus* infections in a maternity department. (F. A. Knott & J. B. Blaikley) 386-400
Treatment of amenorrhoea with combined anterior pituitary follicle-stimulating hormone and chorionic gonadotrophin. (A. Davis) 401-407
Premature birth (analysis of 1,000 cases): incidence, ætiology and immediate result to the baby. (S. C. Sandifer) 408-415
Some curiosities of mammalian reproduction. Part I. Mammals that have triumphed over anatomical handicaps. (F. W. Jones) 416-437
The ætiology of the toxæmias of late pregnancy. (F. J. Browne) 438-471

51 : December 1944

- Carcinoma of the ovary. (I. G. Williams) 489-494
A case report of the effect of hysterectomy on ovarian activity in the female baboon. (J. Gillman & C. Gilbert) 495-498
Prophylactic use of pneumoperitoneum in the puerperium of tuberculous patients. (P. Dingle) 499-508
Report on 130 consecutive cases of placenta prævia without maternal death. (J. Morgan) 509-511
Cholechochus cyst complicating pregnancy and the puerperium. (J. T. Chesterman) 512-518
An analysis of 90 cases of transplantation of the ureters for obstetrical vesicovaginal fistula. (M. Roberts) 519-525
Artificial insemination: report on 80 cases. (I. Halbrecht) 526-528
Recurrent anencephaly: a case report with a note on the ætiology of anencephaly and allied malformations. (H. G. Dunn & J. G. Salter) 529-536
Separation of the symphysis pubis during delivery by the forceps. (D. W. James) 537-540
A case of rupture of the marginal sinus of the placenta. (W. H. Carlisle) 541-542
An unusual case of obstructed labour due to the umbilical cord. (J. P. Maxwell) 543
Double monster. (G. J. Himonides) 544-545
Atresia of œsophagus and imperforate anus communicating with the bladder. (E. Friedmann) 546-548
A case of acute hydramnios successfully treated by abdominal paracentesis. (J. P. Erskine) 549-551
Transposition of the ovarian veins. (A. Roberts) 552
Some curiosities of mammalian reproduction. Part 2. Concerning the life of the sperm. (F. W. Jones) 553-564
Edward Rigby. A chapter in the history of antepartum hæmorrhage. (J. H. Young) 565-568

Journal of Physiology

103 : September 1944

- The effect of morphine and hyoscine on dye concentration curves in plasma volume determination. (R. G. Bowler, A. C. Crooke & C. J. O. R. Morris) 137-141
The behaviour of the cervix uteri *in vivo*. (J. Adler, G. H. Bell & J. A. C. Knox) 142-154
The excretion of histamine in urine. (G. V. Anrep, M. S. Ayadi, G. S. Barsoum, J. R. Smith & M. M. Talaat) 155-174
Cation antagonism in blood coagulation. (G. D. Greville & H. Lehmann) 175-184
The isolation and identification of a pressor base from normal urine. (M. F. Lockett) 185-232
Further observations on the effects of alloxan on the pancreatic islets. (J. S. Dunn, E. Duffy, M. K. Gilmour, J. Kirkpatrick & N. G. B. McLetchie) 233-243
Hyperpnœa in man produced by sudden release of occluded blood. (J. N. Mills) 244-252

103 : December 1944

- Investigations on muscle atrophies arising from disuse and tenotomy. (J. C. Eccles) 253-266

Absolute muscle force in the ankle flexors of man. (H. A. Haxton) 267-273
The acid-labile CO₂ in mammalian muscle and the pH of the muscle fibre. (E. J. Conway & P. J. Fearon) 274-289
The action of adrenaline and of choline-esters on the uterus of the sheep. (J. A. Gunn) 290-296
Liberation of histamine during reactive hyperaemia and muscle contraction in man. (G. V. Anrep, G. S. Barsoum, S. Salama & Z. Souidan) 297-305
Emulsification of fat in the intestine of the rat and its relationship to absorption. (A. C. Frazer, J. H. Schulman & H. C. Stewart.) 306-316
Observations on some conditions affecting the rate of hormone output by the suprarenal cortex. (M. Vogt) 317-332
The inhibition of histamine release by a pituitary-adrenal mechanism. (G. Ungar) 333-343
An optical method for recording peripheral blood pressures and pulse rates in unanesthetized and in anesthetized rabbits. (C. B. B. Downman, C. C. Mackenzie & B. A. McSwiney) 344-349
The effects of acute hemorrhage on the peripheral blood pressure in unanesthetized and in anesthetized rabbits. (C. B. B. Downman, C. C. Mackenzie & B. A. McSwiney) 350-357

Journal of Tropical Medicine and Hygiene

47 : October-November 1944

The surgical treatment of elephantiasis. (G. Bankoff) 49-53
Amoebic infection of the vulva complicating granuloma pudendi. (J. B. Cleland) 54-55
Problems connected with the employment of natives in industry. (F. G. Cawston) 55-56

Lancet

2 : 21/10/44

The conservative treatment of abdominal wounds. (C. G. Rob) 521-522
New drugs active in the chemotherapy of experimental gas gangrene. (D. G. Evans, A. T. Fuller & J. Walker) 523-527
Desert climate: physiological and clinical observations. (W. S. S. Ladell, J. C. Waterlow & M. F. Hudson) 527-531
Congenital absence of sweat glands. (D. H. G. MacQuaide) 531-532
Tragedy of malignant melanoma. (M. C. Tod) 532-534
Venous spasm preventing blood transfusion. (J. G. Humble & G. Belyavin) 534-535
Sulphanilamide poisoning with cerebral manifestations. (H. Reed) 535-536
Evaluation of nutritional state in children. (W. Kornfeld & E. Nobel) 543

2 : 28/10/44

Sulphonamide dermatitis: further observations with special reference to treatment and prevention. (B. C. Tate & J. Klorfain) 553-557
Dysentery in British prisoners of war. (H. Bloom) 558-560
Fatty diarrhoea in chronic and relapsing dysentery. (H. T. Howat) 560-561
Surgery of varicose veins. (H. R. Arthur) 561-562
Pulsator treatment of crush injury. (D. V. Marshall) 562-563
The Sims test. (M. Barton & B. P. Wiener) 563-565
Quinine blindness. (I. S. McGregor & A. Loewenstein) 566-567
Normal death-rate of the Navy. (M. Greenwood & E. Lewis-Fanning) 574-575

2 : 4/11/44

The film in medical education. I. Planning. (C. J. Longland & R. MacKeith) 585-588
The film in medical education. II. Production and scope. (B. Stanford) 588-590
Carbon tetrachloride nephrosis. (J. R. Forbes) 590-592
Segments and blood-vessels of the lungs. (A. B. Appleton) 592-594
Rh antenatal testing: a suggested nomenclature. (J. Murray) 594-596
Tetany after extensive gut resection. (J. A. Cosh) 596-597
Survival after removal of twenty feet of intestine. (C. C. Holman) 597
Cellulitis due to a haemolytic streptococcus type C. (B. Portnoy & R. Reiter) 597-598
Rapid test for the serodiagnosis of syphilis. (F. Rappaport & F. Eichhorn) 599

2 : 11/11/44

Social medicine: an academic discipline and an instrument of social policy. (F. A. E. Crew) 617-619
Micro-methods of estimating penicillin in blood serum and other body fluids. (A. Fleming) 620-621
Penicillin content of blood serum after various doses of penicillin by various routes. (A. Fleming, M. Y. Young, J. Suchet & A. J. E. Rowe) 621-624
Case of African sleeping sickness. (J. Grant, M. Anderson & R. B. Thompson) 624-625
Operation for hydrocele. (H. J. Croot) 625-626

2 : 18/11/44

Lung abscess: pathology and diagnosis of certain types. (N. R. Barrett) 637-651
Direct laryngoscopy and tracheal intubation. (F. B. Bannister & R. G. Macbeth) 651-654
Paroxysmal and postural headaches from intraventricular cysts and tumours. (W. Harris) 654-655
Deficiency diseases in Hong-Kong. (P. B. Wilkinson) 655-658
Alloxan diabetes in monkeys. (S. Banerjee) 658-659
Fatal coronary sclerosis in a boy of ten years. (E. Jokl & J. Greenstein) 659
Resettlement: the end of workmen's compensation. (R. Watson-Jones) 666-667

2 : 25/11/44

Psychosomatic factors in cutaneous disease. (R. M. B. MacKenna) 679-681
Smallpox in the Middle East: lessons from 100 cases. (R. S. Illingworth & W. A. Oliver) 681-685
Use of the Both respirator to reduce postoperative morbidity. (W. W. Mushin & N. Faux) 685-686
Traumatic subdural effusion in children. (J. P. Lanigan) 686-687
Comparison of sulphonamides in bacillary dysentery. (D. G. Ferriman & G. K. Mackenzie) 687-688
Changes in the marrow smear in early megaloblastic hyperplasia. (M. L. Thomson) 688-689
Vaccination against smallpox: apparent anomalies in protection afforded. (W. D. H. Stevenson) 697-700

2 : 2/12/44

Control of venereal diseases: an epidemiological approach. (J. E. Gordon) 711-715
Gramicidin S: origin and mode of action. (G. F. Gause & M. G. Brazhnikova) 715-717
Chemistry of gramicidin S. (A. N. Belozersky & T. S. Passhina) 716-717
Clinical use of gramicidin S. (P. G. Sergiev) 717-718
Amoebic dysentery: facts and fallacies in radical treatment. (P. Manson-Bahr) 718-720
Rodent ulcer treated by application of sodium bicarbonate. (D. Cameron) 720-722

2 : 9/12/44

The voluntary hospital with an undergraduate school. (T. B. Layton) 743-745
Arteriography of peripheral vessels: technical details. (J. R. Learmonth) 745-746
Cancellous chip bone-grafts: report on 75 cases. (R. Mowlem) 746-748
Pyloric stenosis: selective medical and surgical treatment. (N. M. Jacoby) 748-749
Localization of foreign bodies. (J. F. Brailsford) 749-751
Diphtheria APT: immunity response and interval between injections. (G. Bousfield) 751-753
Anaesthesia of anterior ethmoidal nerve after head injury. (A. Wardale) 753

2 : 16/12/44

Inhalation of chemotherapeutic substances. (N. Mutch) 775-780
Infective dermatoses treated with penicillin. (P. H. Taylor & K. E. A. Hughes) 780-784
Nomogram for correcting Sahli haemoglobinometer readings. (G. H. Bell & M. L. McNaught) 784
Prognosis after successful pneumonectomy. (J. M. Cheale & F. H. Young) 784-785
Pregnancy after pulmonary lobectomy. (A. G. Bryce & E. M. Mills) 786

2 : 23/12/44

Traumatic uraemia: reports on eight cases. (E. M. Darmady, A. H. M. Siddons, T. C. Corson, C. D. Langton, Z. Vitek, A. W. Badenoch & J. C. Scott) 809-812
Deficiency bowel pattern in Polish refugees, African and Indian adults and children (Kwashiorkor). (J. S. Brown & H. C. Trowell) 812-816
Better drainage for non-tuberculous empyema. (A. K. Henry) 816-817
Congenital subluxation of acromioclavicular joint. (J. Grieve) 817-818
Fluorescence microscopy in the detection of tubercle bacilli. (H. Lempert) 818-822
Delayed rupture of the spleen. (L. Gillis) 822-823
Autograft of amputated thumb. (S. Gordon) 823
Septicæmia due to *Bact. necrophorum* and an anaerobic streptococcus. (H. P. Jones) 824

2 : 30/12/44

Epidemiology of peptic ulcer: vital statistics. (J. N. Morris & R. M. Titmuss) 841-845
Treatment of early syphilis with penicillin. (A. O. F. Ross, R. B. Nelson, E. M. Lourie & H. O. J. Collier) 845-848
Octyl nitrite in achalasia of the cardia. (C. E. Field) 848-851
Fracture of the odontoid process: a method of fixation. (E. H. T. Hambly) 851
Typhoid septicæmia: report of a case. (J. F. Goodall) 851-852

Nutrition Abstracts and Reviews

14 : July 1944

Nucleic acids and tissue growth. (J. N. Davidson & C. Waymouth) 1-18

14 : October 1944

The water economy of farm animals. (I. Leitch & J. S. Thomson) 197-223

Proceedings of the Royal Society, B

132 : December 1944

Thyroxine: its biosynthesis and its immunochemistry. Croonian Lecture. (C. R. Harington) 223-238
Studies on temperature regulation. I. The Pulmonata and Oligochaeta. (L. Hogben & R. L. Kirk) 239-252
The effect of hypoxanthine on the growth of an avian tissue *in vitro*. (F. G. Hopkins & I. Simon-Reuss) 253-257
The ecological determinants of population growth in a *Drosophila* culture. I. Fecundity of adult flies. (F. W. Robertson & J. H. Sang) 258-277
The ecological determinants of population growth in a *Drosophila* culture. II. Circumstances affecting egg viability. (F. W. Robertson & J. H. Sang) 277-291
The visual perception of movement by toads. (H. Honigsmann) 291-307
The genetical activity of heterochromatin. (K. Mather) 308-332

Proceedings of the Royal Society of Medicine

38 : November 1944

A half-century of serology. President's Address, Section of Comparative Medicine. (H. J. Parish) 1-6
Edward Bancroft, M.D., F.R.S., and the War of American Independence. (A. S. MacNalty) 7-15
John Zephaniah Holwell (1711-1788) and the Black Hole of Calcutta. (H. P. Bayon) 15-18
Pathology. President's Address, Section of Pathology. (W. G. Barnard) 19-24
Genital tuberculosis. President's Address, Section of Urology. (F. McG. Loughnane) 25-30
Notes on glaucoma. President's Address, Section of Ophthalmology. (P. E. H. Adams) 31-36
Jacobson's organ. President's Address, Section of Odontology. (H. T. Roper-Hall) 41-50

Public Health

57 : September 1944

Diphtheria immunisation: observations on prophylactics and duration of immunity. (A. Anderson) 131-135
Venereal diseases in a large port. (A. O. F. Ross) 135-136
Problem families. (R. C. Wolfenden) 136-139

58 : October 1944

The country doctor and public health. (W. N. Pickles) 2-5
Diphtheria immunization in a rural area of New Zealand. (C. W. Dixon) 5-6
Mass radiography at the cross roads. (E. G. W. Hoffstad) 7-8

58 : November 1944

The school medical service. (J. C. Ede) 12-15
What is a health centre? (I. H. Pearce) 15-18
Trace elements in relation to health. (C. F. Brockington) 19-21

58 : December 1944

The medical officer of health. (R. M. F. Picken) 28-29
On the incidence of scabies. (T. M. Clayton) 29-35
The future of the school medical officer. (F. J. G. Lishman) 35-36

Quarterly Journal of Experimental Physiology

33 : 1944

Biological assay and standardisation of melanophore expanding pituitary hormone. (F. W. Landgrebe & H. Waring) 1-18
Factors in pancreatin which influence the nucleoprotein content of fibroblasts growing *in vitro*. (J. N. Davidson & C. Waymouth) 19-33
Serum choline esterase in barbiturate addiction and epilepsy. (F. Schütz) 35-52
The production of renal failure following injection of solutions containing myohæmoglobin. (E. G. L. Bywaters & J. K. Stead) 53-75
On the metabolism of histamine. (F. Alexander) 71-76

Quarterly Journal of Medicine

13 : April-July 1944

'Fibrositis' of the back. (W. S. C. Copeman & W. L. Ackerman) 37-51
Proteolysed liver in the treatment of refractory anaemias. (L. J. Davis & L. S. P. Davidson) 53-73
A critical review of pernicious anaemia of pregnancy. (S. T. E. Calder) 75-105

Quarterly Journal of Pharmacy & Pharmacology

17 : July-September 1944

- The education of the pharmacist. (H. Brindle) 155-164
The sterilising action of steam admixed with air and other gases. (R. M. Savage) 165-171
The protection of ether against peroxide formation. (E. Boehm & R. Williams) 171-177
The stability of preparations containing ethyl nitrite. (A. H. A. Abbott & B. H. Hooper) 177-182
Vitamin B in malt extract. (J. G. Organ, E. M. James & F. Wokes) 183-187
The stability of vitamin C in blackcurrant syrup. (F. Wokes & J. G. Organ) 188-196
Rose hip tablets. (F. Wokes, E. H. Johnson & F. C. Jacoby) 196-201
The histology of belladonna root. I. *Atropa belladonna* Linn. (C. Melville) 201-213
The histology of belladonna root. II. Indian belladonna. (C. Melville) 213-220
The analysis of the pastilles of the British Pharmaceutical Codex. (N. Evers & W. Smith) 220-225
A note on the hydrolysis of diamorphine hydrochloride in aqueous solution. (G. A. Storey) 225-226
The determination of hyoscine, hyoscyamine and atropine. (J. M. Rowson) 226-233
The assay of belladonna and of some other solanaceous drugs—determination of hyoscyamine, atropine and hyoscine. (J. M. Rowson) 234-237
Biological assays of simple adrenaline solution by the cat and frog heart methods. (H. Berry, E. Shotton & G. B. West) 238-241
The stability of adrenaline solutions. I. Solutions of adrenaline hydrochloride. (H. Berry & G. B. West) 242-248

The preparation of compressed tablets. II. The measurement of the rate of disintegration by a shaking method. (H. Berry & A. N. Smith) 248-256

Transactions of the Royal Society of Tropical Medicine and Hygiene

38 : November 1944

- Cholera incidence in India in relation to rainfall, absolute humidity and pilgrimages; inoculation of pilgrims as a preventive measure. (L. Rogers) 73-94
Malaria survey of the Dead Sea area during 1942, including the description of a mosquito flight test and its results. (J. M. Shapiro, Z. Saliternik & S. Belferman) 95-116
Infant mortality in the British West Indies. (P. G. Edge) 117-132
Typhus research in Egypt, Palestine, Iraq and Iran. (C. E. van Rooyen, J. H. Bowie & K. S. Krikorian) 133-149
The chemotherapy of experimental leishmaniasis. I. The spleen as an index of infection in the Syrian hamster. (K. G. Goodwin) 151-160
A case of blackwater fever in an African girl. (J. O. Shircore) 161-162

38 : December 1944

- Spray-killing of mosquitoes in houses—a contribution to malaria control on the Gold Coast. (L. G. Eddey) 167-197
Pyrethrum as a tsetse fly repellent: human experiments. (J. R. Holden & G. M. Findlay) 199-204
Rough notes: *Anopheles* mosquitoes and malaria in Arabia. (P. A. Buxton) 205-214
Observations on *Anopheles gambiae* and other mosquitoes at Wadi Halfa. (D. J. Lewis) 215-229
Yellow fever in the recently inoculated. (M. Elliott) 231-234

Erratum

In BMB 491 (Vol. 2 No. 10-11) for pyroxidin read pyridoxine

